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MULTIPLE CANCERS: PRIMARY IN THE LUNG AND OTHER SITES

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THE occurrence of more than one primary cancer in the same individual is no longer a medical curiosity. Numerous references attest to the frequency with which this phenomenon has appeared, both in life and at autopsy, and up to 1932, 1,259 instances had been reported.[7] These multiple lesions have been known to group themselves in organs that are part of an anatomic or physiologic system, but they are also frequently found in sites that have no particular interrelationship.

Warren and Gates[7] performed 2,829 autopsies on patients with cancer and found 194 instances of multiple primary malignant growths—an incidence of 6.8 per cent. On the basis of these data, they concluded that "an individual with one cancer is more apt to develop a second cancer than would be expected by chance alone." This tendency was considered to be eleven times greater than that of a patient without cancer to develop his first lesion. The authors also stated that an average interval of 3.2 years elapsed between the appearance of the individual neoplasms, when this could be measured.

If this predisposition to develop multiple malignant tumors exists in certain individuals, it is reasonable to suppose that as survival rates are extended by a combination of earlier diagnosis and improved methods of treatment, new cancers can be expected to arise in new sites. Therefore, in follow-up examinations, patients who have had cancer should be scrutinized for evidence of a separate primary growth as well as for metastases from a lesion already known to exist.

The management of multiple primary cancers may seem at first to be exceedingly complex. Indeed, in those occurring synchronously, it is often difficult to decide what form of therapy to employ and which tumor deserves first consideration therapeutically or if both should be treated at once. In metachronous lesions there is less confusion, for the time interval between the appearance of the separate tumors usually permits an estimation of the

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degree of control of the first lesion and a more deliberate selection of the treatment for the second.

Admittedly, the possibility of survival diminishes with the advent of each new cancer capable of metastasizing. Yet, it is more and more suggestive, as experience accumulates, that the maintenance of aggression in treatment, rather than the yielding to defeatism, has produced surprisingly favorable results. Consequently, we feel that the appearance of two, three, or more primary cancers of different organ systems should not contraindicate radical therapy for each. If, for example, an adenocarcinoma of the rectum has been controlled by an abdominoperineal resection and later a carcinoma of the breast develops, it should be treated by radical mastectomy. Similarly, the apparently complete eradication of a malignant testicular tumor several years prior to the appearance of a gastric cancer would not contraindicate gastrectomy.

The probability of survival in each separate case of cancer varies considerably with the particular clinical setting. If the carcinoma of the rectum just mentioned occurred by itself and were in the pathologic classification of Duke's A or Duke's B, the patient would have an estimated 65 to 85 per cent chance of living five years. If the breast cancer that was removed subsequently were the only tumor present and found not to have metastases in the regional lymph nodes, the chance of five-year survival would be approximately 75 per cent. One can only conjecture whether the combination of these two primary lesions in one individual would alter the prognosis. Actually, it may be even better than that reported for cases in which only solitary cancer of the stomach or lung is present.

Patients need psychological help in facing repeated major surgical procedures, but respond well when a reasonable chance of "cure" is offered. Thus, a 49-year-old mother of four children did not protest when she was faced with the necessity of a radical mastectomy, an anterior resection of the sigmoid colon, and a right upper and middle lobe lobectomy—the last two operations within two months of each other.

CRITERIA FOR MULTIPLICITY

Criteria for diagnosis of multiple cancers must be clearly defined. In the first two examples cited previously, carcinoma of the rectum followed by a breast cancer and a malignant testicular tumor followed by a gastric cancer, the combinations of lesions were such that the second primary, because of its location, was not likely to be confused with a metastasis from the first. However, when lung tumors are considered, a careful distinction must be made as to whether this organ is acting as the site of a new growth or as a filter and repository of metastases. This distinction can be made only when the two tumors have entirely different histologic characteristics, as in Case No. 11 (Table III) in which a squamous carcinoma of the hard palate coexisted with an adenocarcinoma of the lung (Fig. 1). There are seven cases in this series meeting this criterion, and these are classified as having *positive* evidence of multiple primary cancers.

On the other hand, if the two lesions in question have the same histologic pattern, it is almost impossible to distinguish microscopically between a primary focus and a metastasis in the lung. By no means, however, does this necessarily exclude the possibility that the pulmonary lesion may be a separate and distinct primary. Reliance in these instances must be placed upon the clinicopathologic picture, and in this series, thirteen cases are classified as having *probable* evidence of multiple primary cancers. In Case No. 20, squamous carcinoma existed synchronously in the extrinsic larynx and the left main bronchus. The latter is an unusual site for metastasis from the former, and, in

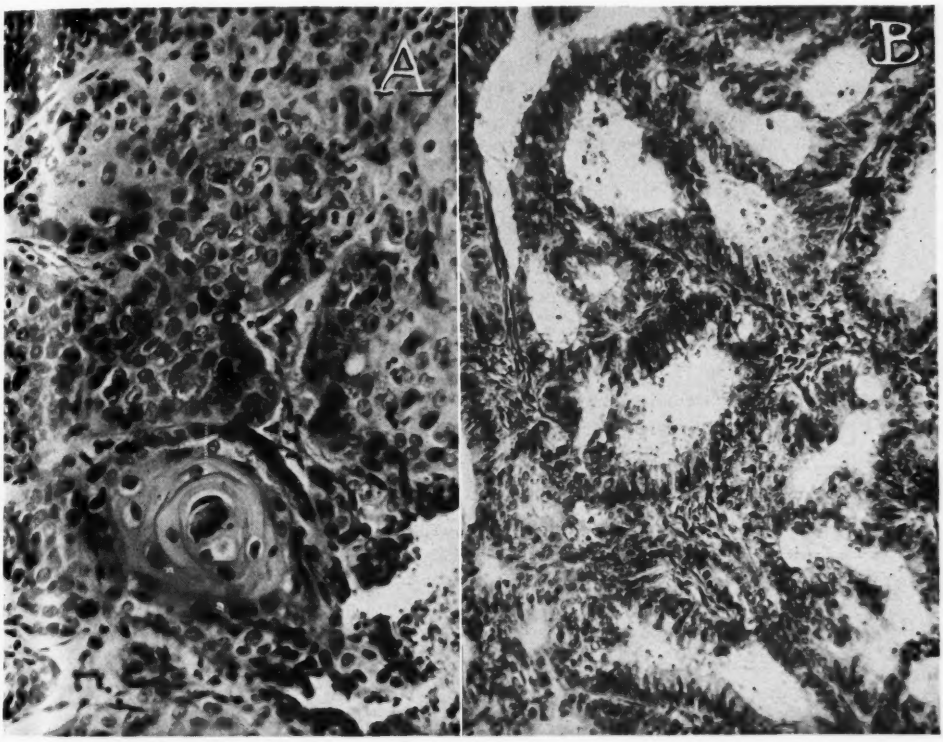

Fig. 1 (Case No. 11).—*A*, Squamous carcinoma of the hard palate, and *B*, adenocarcinoma of the lung, in the same patient.

the gross specimen removed by total pneumonectomy, a cancer was found arising from the bronchial wall. There were no metastases noted in the remainder of the resected lung, nor have any appeared in the regional lymph nodes or in the opposite lung in the twelve months since operation.

In Case No. 13, a squamous carcinoma confined to the edge of one vocal cord and noninfiltrative in character, occurred synchronously with an epidermoid carcinoma of the right upper lobe bronchus. The pathologist felt that

the probability that the two lesions represented a primary cancer and its metastasis was remote, despite the presence of the same basic histologic pattern.

In a separate group are five cases of lung cancer associated with basal cell carcinomas of the skin. Although these skin cancers are nonmetastasizing, their presence in combination with another malignant growth stresses the possible inherent tendency of some individuals to evolve cancer.

COMPILATION OF CASES

In 1,493 cases of cancer of the lung observed in Memorial Hospital over a period of twenty-four years, there have been twenty-five instances in which the lung tumor was one of two or more separate primary malignant growths—an incidence of 1.6 per cent (Table I). There was one triple primary. Warren and Gates[7] found 120 lung cancers in their autopsy series, in nine of which there was another primary lesion—an incidence of 7.5 per cent. The constituted 4.6 per cent of all the cases found at autopsy to have multiple primary cancers.

TABLE I. MULTIPLE PRIMARIES ASSOCIATED WITH LUNG CANCER
From the Files of Memorial Hospital

Total cases of lung carcinoma	1,493
Total multiple primaries	25
Incidence	1.6%

The sites of the separate malignant growths in our series are listed in Table II and include seven of the oral cavity, four of the larynx, two of the rectum, and one each of the breast, uterus, bladder, kidney, and thyroid. There was one case in which the lung cancer was combined with lymphatic leucemia and five cases where it occurred with basal cell carcinomas of the skin. The triple primary included cancers of the breast and sigmoid and is listed separately.

TABLE II. MULTIPLE PRIMARIES ASSOCIATED WITH LUNG CANCER

	DOUBLE PRIMARY
Oral cavity	7
Skin	5
Larynx	4
Rectum	2
Kidney	1
Bladder	1
Breast	1
Uterus	1
Thyroid	1
Lymphatic leucemia	1
Total	24
	TRIPLE PRIMARY
Breast and sigmoid	1
Total Cases	25

In the literature[5, 6, 7, 8] there are at least thirty-seven cases in which, at autopsy, a cancer of the lung has been found to be one of two malignant tumors; of these the kidney, colon, and stomach were the sites of the other tumor five times; the skin, four times; the prostate and breast, three times each; the esophagus, gall bladder, and tongue, twice each; and the lip, bladder, larynx, liver,

sarcoma of the leg, and lymphosarcoma, once each. In addition, there was a triple primary arising synchronously as a squamous carcinoma of the bronchus, adenocarcinoma of the pancreas, and carcinoma of the prostate.

In a discussion of multiple primary malignant growths, the time relationships between the appearances of the tumors is of interest. In this communication, the cancers are considered synchronous if the interval between the establishment of the diagnosis of the first primary tumor and the detection of the second was less than six months; metachronous, if more than six months. In our twenty-five cases, the lung cancer was synchronous with another malignant tumor in fifteen instances—twelve of these in combination with a cancer capable of metastasizing—and in ten cases, the lung cancer appeared at least twelve months after the discovery of the first tumor. In not one instance did the lung lesion antedate the appearance of the second growth by any significant length of time, probably because the early mortality of patients with cancer of the lung precluded their propagating second lesions. This situation occurs also among the cases reported in the literature, in which the lung tumor was usually the last of the primary growths to appear in an individual.

DIAGNOSIS

When a patient who has a cancer known to metastasize develops pulmonary symptoms or an asymptomatic roentgenographic shadow suggestive of primary lung cancer, the problem of establishing the true nature of the process is vital and often requires considerable clinical and laboratory data.

History and Physical Examination.—In only one case was mention made of cancer in a member of the immediate family, but this item on the patients' histories was usually incomplete.

Although a primary cancer of the lung may be expected to show earlier evidences of bronchial irritation and compression than a metastasis, little reliance can be placed on signs and symptoms as aids in differentiating between the two. In this series, it was largely in the metachronous lesions that the symptoms of cough and hemoptysis directed attention to the lung.

There were twenty men and five women in this series. Their ages varied from 49 to 80 years, with an average of 62 years. The youngest patient was a 49-year-old woman who had three separate primary tumors.

Roentgenographic Findings.—Eight cases were detected following routine roentgenograms of the chest taken either as part of a check-up examination or to determine whether multiple lung metastases were present. The value of chest films at six or twelve-month intervals as part of a follow-up system cannot be overestimated.[4] Lesions discovered before symptoms develop are more likely to be resectable.

The correct diagnosis was suggested roentgenographically in ten instances. Primary lung cancer was suspected for the following reasons: the infrequency with which certain cancers metastasize to the lung, and the shape of the shadow, usually associated with a segmental atelectasis. It is felt, however, that the most important element is the alertness of the radiologist to the fact that a density in the lung *may* represent a new primary carcinoma and not necessarily a metastasis.

TABLE III

NAME AGE SEX	FAMILY HISTORY (CA.)	FIRST PRIMARY: PATHOLOGY	SITE	YEAR TREATED	METHOD	TIME INTERVAL (YEARS)	LUNG PRIMARY: FIRST SYMPTOM	DIAGNOSIS ESTABLISHED	PATHOLOGY	TREATMENT	FOLLOW-UP
Metachronous Multiple Primaries											
1. W. H. 54 M	+	Adenoca. gr. 3 nodes clear	Rectum	1940	A-P resection	8	Hemoptysis	Pap. IV, x-ray	Bronchiogenic Ca. nodes clear	Pneumonectomy 7/49	N.E.D.* 8 mos. 3/50
2. J. H. 63 M	0	Adenoca. gr. 2 nodes clear	Rectum	1937	A-P resection	10	Cough	Pap. V, x-ray	Sq. Ca. gr. 2	X-ray therapy 1948	D.O.D.† 1948
3. E. B. 58 F	0	Infiltrating Duct Ca.	Breast	1946	Rad. mastectomy	3	Chest pain	X-ray aspir. biopsy	Bronchiogenic epid. gr. 3 positive nodes	Pneumonectomy 8/49	D.O.D. 10/49
4. M. G. 56 F	0	Endomet. Ca.	Uterus	1943	Hysterectomy	3	Cough	X-ray, biopsy	Bronchiogenic Ca.	X-ray therapy 2/46	Died 7/46 cerebr. met.?
5. A. B. 71 M	0	Papillary epid. gr. 1	Bladder	1941	Resection	2	Hemoptysis	Biopsy	Bronchiogenic Ca. gr. 2	Radon applicator 12/42	Died uremia 12/43 12 mo.
6. C. G. 65 F	0	Lymphatic	Leucemia	1945	X-ray P-32	5	Cough	X-ray, Pap. V	Bronchiogenic Ca. Metastases to liver (autopsy)	X-ray 6/49	D.O.D. 3/50
7. M. McT. 52 F	0	Sq. Ca.	Buccal mucosa	1948	X-ray excision	1	Cough	X-ray, Pap. V	Sq. Ca. lung gr. 2 Pos. intrapulmonic node	Pneumonectomy 9/49	Evid. met. 3/50

8. R. K. 60 M	0	Basal cell	Skin	1948	X-ray	2	Cough	X-ray Pap. V	Bronchiogenic Ca.	X-ray 2/50	D.O.D. 4/50 2 mo.
9. S. C. 46 M	0	Basal cell	Skin	1927	Excision	8	Cough	X-ray biopsy	Epid. Ca. gr. 2	X-ray 10/36	D.O.D. 12/36 2 mo.
					TRIPLE PRIMARY						
10. A. C. 40 F	0	1. Infiltr. Duct Ca. pos. nodes 2. Adenoca. gr. 2 Duke's B	Breast Sigmoid	5/41 9/49	Rad. mastectomy Sigmoidectomy	8 2 mo.	Routine x-ray	X-ray Pap. III	Bronchiogenic Ca. bronchiolar type	11/49 R.U.L. and R.M.L. lobectomy	3/50 N.E.D. 4 mo.
					Synchronous Multiple Primaries						
11. W. B. 55 M	0	Sq. Ca. gr. 2	Palate	8/49	X-ray	0	Routine x-ray	X-ray Pap. V	Bronchiogenic adenoca. neg. nodes	9/49 Pneumonectomy	D.O.D. 2/50
12. J. G. 80 M	0	Epid. Ca. gr. 3	Intrinsic larynx	2/48	Laryngectomy	0	Routine x-ray	X-ray Pap. V	Epid. Ca. gr. 2	4/48 Intracavitary radium	N.E.D. 18 mo. 10/49
13. T. McC. 56 M	0	Epid. Ca. gr. 2 in situ	Intrinsic larynx	4/48	Partial laryngectomy	0	Cough and hemoptysis	Pap. V x-ray	Epid. Ca. gr. 3 positive nodes	5/48 R.U.L. and R.M.L. lobectomy	11/48 died ? chest neg.
14. R. McA. 68 M	0	Basal cell	Skin	8/48	Excision	0	Hemoptysis	Aspir. biopsy, x-ray, Pap. III	Epid. Ca. gr. 3	7/48 Pneumonectomy	3/50 N.E.D. 20 mo.
15. R. P. 65 M	0	Sq. Ca. gr. 1	Tongue	9/47	Glossectomy	0	Routine x-ray	Pap. V biopsy	Epid. Ca.	9/47 X-ray	D.O.D. 4/48 7 mo.
16. A. R. 65 M	0	Sq. Ca. gr. 2	Gingiva	9/44	X-ray	0	Routine x-ray	X-ray biopsy	Sq. Ca. gr. 2 of trachea	10/44 X-ray	D.O.D. 5/45 7 mo.

†Died of disease
•No evidence of disease.

TABLE III—CONT'D

FIRST PRIMARY							LUNG PRIMARY				
NAME AGE SEX	FAMILY HISTORY (CA.)	PATHOLOGY	SITE	YEAR TREATED	METHOD	TIME INTERVAL (YEARS)	FIRST SYMPTOM	DIAGNOSIS ESTABLISHED	PATHOLOGY	TREATMENT	FOLLOW-UP
17. G. K. 68 M	0	Sq. Ca. (Early)	Vocal cord	1/48	Cordectomy	0	Routine x-ray	X-ray Pap. V	Epid. Ca.	2/48 Thoracotomy and x-ray	D.O.D. 5/49 13 mo.
18. E. H. 56 M	0	Epid. Ca.	Renal pelvis	7/47	Nephrectomy	0	Hemoptysis	X-ray Pap. V	Epid. Ca. gr. 2 nodes clear	12/46 Pneumonectomy	D.O.D. 12/47 12 mo.
19. J. R. 65 M	0	Sq. Ca. gr. 2	Gingiva	10/39	X-ray	2 mo.	Cough	Biopsy	Epid. Ca.	8/40 X-ray	D.O.D. 9/40 1 mo.
20. L. B. 64 M	0	Sq. Ca. gr. 2	Larynx	5/49	Laryngectomy	0	Routine	X-ray Pap. III	Sq. Ca. gr. 2 nodes clear	3/49 Pneumonectomy	3/50 N.E.D. 12 mo.
21. J. H. 62 M	0	Basal cell	Skin axilla	12/43	Excision	0	Cough	X-ray node	Epid. Ca.	12/43 X-ray	3/44 D.O.D. 3 mo.
22. A. O. 70 M	0	Sq. Ca. gr. 2	Flr. of mouth	10/42	X-ray	0	Routine	X-ray biopsy	Epid. Ca.	11/42 X-ray	D.O.D. 12/42 1 mo.
23. R. L. 35 M	0	Ca.	Thyroid	9/43	Asp. mass	0	Chest pain	X-ray biopsy	Bronchiogenic Ca.	X-ray 9/43	D.O.D. 11/43 2 mo.
24. J. C. 65 M	0	Epid. Ca.	Tongue	1/46	X-ray	0	Cough	X-ray biopsy	Epid. Ca.	X-ray 2/46	D.O.D. 4/46 2 mo.
25. C. H. 77 M	0	Basal cell	Skin	8/47	X-ray	0	Chest pain	X-ray aspir. biopsy Pap. V	Epid. Ca.	X-ray 8/47	D.O.D. 12/47 4 mo.

Additional aid in diagnosing asymptomatic shadows may be derived from previous chest roentgenograms. Tomography will help to reveal bronchial changes in the absence of atelectasis, and, of course, serial roentgenograms will show changes and new lesions. A delay of even three weeks, however, waiting for a significant alteration on the appearance of a shadow or for a new metatasis may convert a resectable to a nonresectable lung cancer.

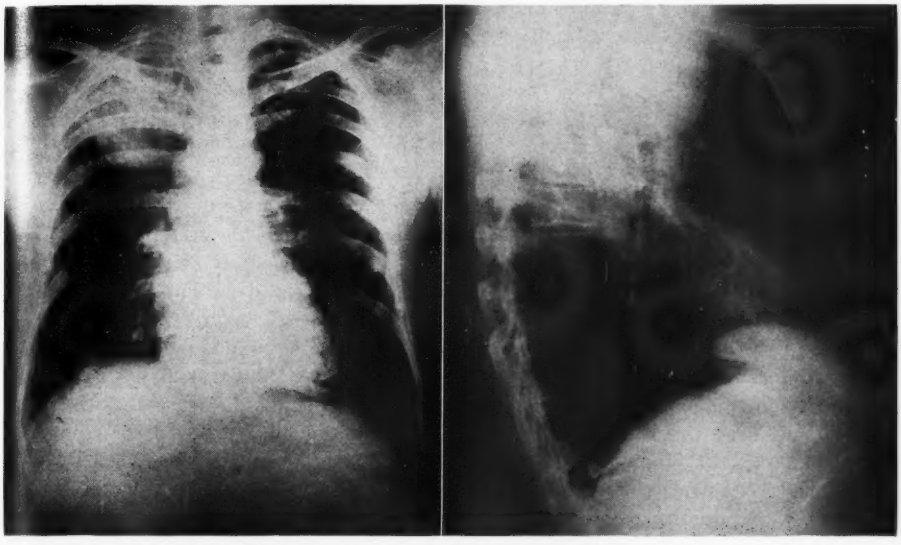

Fig. 2 (Case No. 11).—Posteroanterior and lateral chest roentgenograms, showing shadow and partial atelectasis of right upper lobe.

Bronchoscopy and Exfoliative Cytology.—Effler, Blades, and Marks[2] have stated that it is almost impossible to determine the exact nature of an asymptomatic lung tumor before it is excised. Nevertheless, in four cases, it was possible to make a presumptive preoperative diagnosis of primary lung cancer by obtaining histologic material that differed from the second cancer. In two cases (No. 2 and 11) this was accomplished by exfoliative cytological studies, stained according to the method of Papanicolaou; in another case (No. 4) by biopsy during bronchoscopy; and in still another (No. 3) by aspiration biopsy.

Sputum and bronchial washings stained for malignant cells in particular aid the diagnosis of peripheral lesions that are detected roentgenographically. These are usually early growths and are not accessible to bronchoscopic vision. In Case No. 2, a correct diagnosis was made when the first cancer was an adenocarcinoma of the rectum and the cytologic picture of the bronchial washings was squamous carcinoma. A total pneumonectomy was performed and the diagnosis of bronchiogenic carcinoma was confirmed.

Dr. Papanicolaou[3] states that in sputum or bronchial aspirate containing clusters of cells the varieties of primary lung cancer can often be distinguished. Approximately 85 per cent of all lung cancers can be diagnosed by cytology studies. On the other hand, metastases tend to yield scanty exfoliations and a lessened opportunity for cytologic diagnosis. Further studies are being made which may help to clarify this problem.

Biopsy at Operation.—In two cases (No. 10 and 20) final diagnosis was derived from the findings at exploratory thoracotomy. Under the equivocal circumstances that surround solitary lung lesions such as were found in these two patients, the lung is carefully examined at operation for signs of multiple parenchymal nodules which might indicate diffuse metastases not demonstrable by roentgenogram. If found, one can usually be excised for histologic examination.

Tumors located near the hilum and seeming to arise in the main-stem bronchus, as in Case No. 20, are considered to be primary lung cancers and a total pneumonectomy is performed for their removal. This provides the only means of securing a complete specimen for histologic study without incising the lesion itself, thereby running the risk of intrapleural dissemination of infection and/or neoplastic tissue.

The problem of distinguishing solitary peripheral lesions from metastasis at exploratory thoracotomy is more difficult. There were six instances (not recorded in this paper) in which metastasis in the lung was found, rather than a primary lung tumor. Various methods were employed in the operating room to help establish their identity so that the appropriate procedure could be performed. Aspiration biopsy of the tumor through the open chest provided tissue for a quick pathologic diagnosis and proved of value only when the histologic report of the primary lesion elsewhere was available for comparison. However, this procedure is now reserved for unresectable lesions, where a biopsy is of academic interest only.

Wedge and segmental resection of the smaller, more peripherally-placed lesions has been used, but it is felt that lobectomy affords a better chance of deciding whether the lesion is a primary tumor of the lung by permitting the study of its relationship to the bronchial tree. In addition, it is a safer procedure because it provides a wider and more complete excision of the tumor. If, upon gross examination of the specimen and the frozen section of the lesion, the presence of a primary lung cancer is established, a total pneumonectomy with hilar and mediastinal lymph node dissection can be performed, although in some clinics, a lobectomy is used as the complete procedure for the treatment of lung cancer confined to one lobe. Should the lesion prove to be a metastasis, nothing further need be done. Many of the thirty-five cases reported in the literature, in which metastatic foci were excised from the lung, obtained good palliation and surprisingly long survival rates.[1]

TREATMENT

Of the twenty-five lung cancers in this series, eleven were surgically explored—seven had pneumonectomies; two, lobectomies; and two were con-

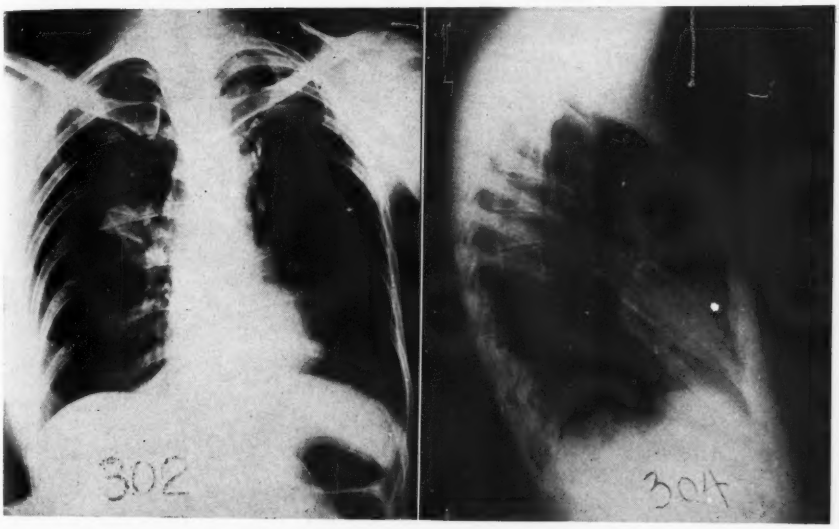

Fig. 3 (Case No. 10).—Triple primary, posteroanterior and lateral views. Chest roentgenograms showing opacity in right upper and middle lobes.

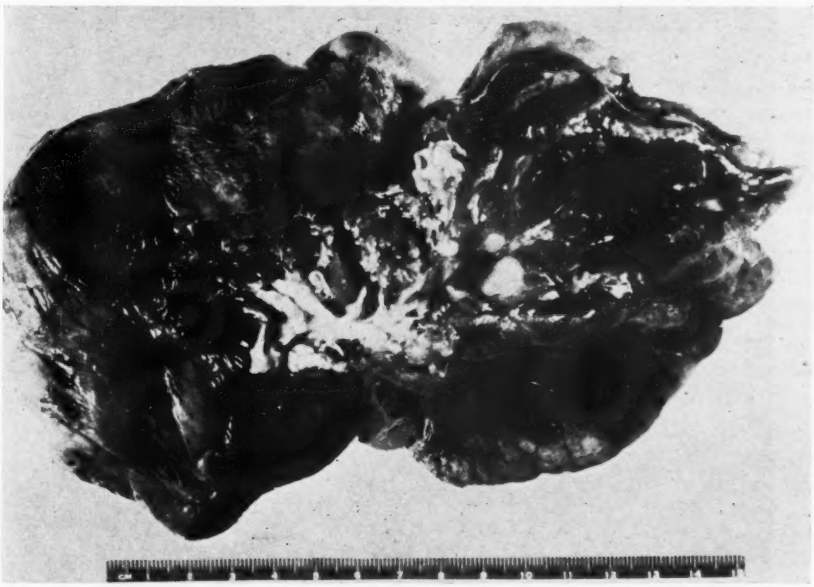

Fig. 4. (Case No. 10).—Triple primary. Right upper and middle lobes containing lesion.

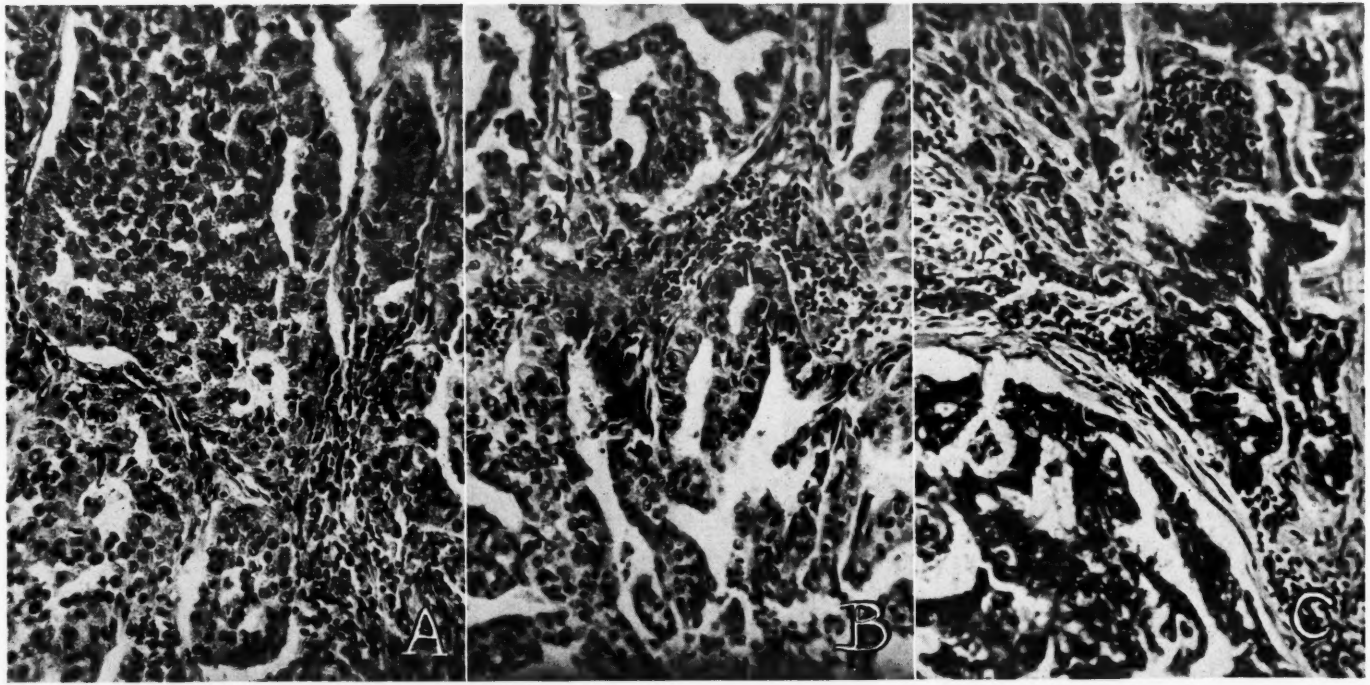

Fig. 5. (Case No. 10).—Photomicrographs of the triple primary malignant tumors: *A*, Infiltrating duct carcinoma, breast; *B*, adenocarcinoma, grade 2, of rectum; *C*, bronchiogenic carcinoma, bronchiolar type.

sidered nonresectable and were subsequently irradiated. It is worth noting that eight of these surgical procedures were performed in the last two years, which fact can be construed as an indication of a more aggressive surgical policy.

Of the nine patients who underwent surgical excision, four died of disease—two, six, eight, and twelve months after pneumonectomy. One patient (Case No. 7) is living six months postoperatively, although there are metastases in the remaining lung. The other four cases are living without evidence of disease—four, eight, twelve, and twenty months after operation—and include a patient with triple primary cancer (Case No. 10) who is living eight years after radical mastectomy, six months after sigmoidectomy, and four months after right upper and middle lobe lobectomy.

Twelve patients were treated only by irradiation and two others were added after exploratory thoracotomy revealed nonresectable lesions. Except for palliative benefits, roentgen-ray therapy was of little value in the prolongation of life, all of these patients dying of extension of the lung cancer within thirteen months of the institution of treatment.

Two cases received local irradiation by the application of intrabronchial, radon-containing, capsules through the bronchoscope. Case No. 5 survived twenty-four months and died of uremia, secondary to the extension of the bladder carcinoma. Chest roentgenogram, taken just prior to death, was reported as negative. One patient, Case No. 12, is alive at present without evidence of extension of the primary carcinomas of the lung and intrinsic larynx, eighteen months after treatment.

Two cases will be described in some detail.

CASE NO. 1.—This patient was a 54-year-old white man who first came to Memorial Hospital on July 19, 1940, with a complaint of rectal bleeding of eight months' duration. Biopsy of a rectosigmoid lesion, 12.5 cm. from the anal margin, was reported to be adenocarcinoma, grade 2. On Oct. 24, 1940, a one-stage, combined abdominoperineal resection was performed. On subsequent follow-up visits, the patient was reported to be well, until May 2, 1949, when he complained of slight cough and bloody sputum. Roentgenogram of the chest indicated the possibility of an early bronchiogenic carcinoma. Bronchoscopy had revealed no apparent abnormality. Papanicolaou studies of bronchial washings were reported as Class V, "Conclusive evidence of a squamous carcinoma of the lung." On July 15, 1949, at exploratory thoracotomy, a tumor mass was found in the apex of the left lower lobe, measuring about 4 cm. in diameter, and extending across the interlobar fissure to the left upper lobe. A left pneumonectomy was done and the specimen was reported as bronchiogenic squamous carcinoma—nodes clear. The patient had an uneventful recovery and was without evidence of disease eight months later.

Comment.—The development of metachronous lesions, in this case of the rectum and lung, was separated by nine years, and a preoperative diagnosis of a new primary pulmonary cancer was derived from roentgenograms and bronchial cytologic studies.

CASE NO. 6.—The patient was a 65-year-old white woman, who was first seen on Sept. 29, 1948, presenting a history of lymphatic leucemia of five years' duration. She had been treated elsewhere for the disease by roentgen irradiation, radioactive phosphorus, and urethane. On examination, there was generalized adenopathy and hepatosplenomegaly. White blood count was over 200,000, with 92 per cent lymphocytes. She had no pulmonary

complaints, but a submitted chest roentgenogram taken four months previously showed a 6 cm. opacity in the right lower lung field. This was reported by the radiologist as "consistent with bronchiogenic carcinoma." Bronchoscopy did not visualize the tumor. A sputum specimen was reported as Class V, "Shows large masses of lymphocytes and also clusters of neoplastic cells suggestive of a malignant lung tumor, adenocarcinoma in type." Roentgen-ray therapy to the lung lesion was begun on May 6, 1949, and the patient was given 3,000r. to each of two chest portals, anterior and posterior, using the 1,000 KV. machine. She remained asymptomatic until Feb. 9, 1950, when she complained of marked weakness, nasal hemorrhages, and she developed axillary and inguinal lymph node enlargement. ACTH was administered without avail. She died on March 20, 1950. At autopsy, the diagnosis of terminal alveolar adenocarcinoma of the right lower lobe of the lung, metastatic to liver, was revealed, together with diffuse evidences of lymphatic leucemia.

Comment.—In this instance, radiation therapy was selected as the method of choice because the hemorrhagic propensity of patients with leucemia precluded surgical intervention.

SUMMARY

1. In 1,493 cases of lung cancer at Memorial Hospital, there were twenty-five multiple primary cancers in which the lung was the site of one of the tumors.

2. There were fifteen instances of synchronous and nine of metachronous multiple cancers. One triple primary cancer of the breast, rectum, and lung is included.

3. The relative importance of the methods of establishing a definite diagnosis of the pulmonary lesion has been discussed. The value of routine chest roentgenograms and of exfoliative cytologic studies of bronchial secretions has been emphasized.

4. Radiation therapy has value as a palliative measure in the treatment of the cancer, primary in the lung, but surgical intervention may be preferable, for it serves both as a diagnostic and therapeutic measure.

5. There should be no defeatism engendered by the appearance of a lung shadow in the presence of a known cancer at another site. Rather, aggressive measures directed at establishing the nature of the new growth and eradicating it must be instituted.

REFERENCES

1. Alexander, J., and Haight, C.: Pulmonary Resection for Solitary Metastatic Sarcomas and Carcinomas, Surg., Gynec. & Obst. **85**: 129-146, 1947.
2. Effler, D. B., Blades, B., and Marks, E.: The Problem of the Solitary Lung Tumors, Surgery **24**: 917-928, 1948.
3. Papanicolaou, G.: Personal communication.
4. Pool, J. L., Watson, W. L., and Diamond, H. D.: Asymptomatic Intrathoracic Tumors. To be published.
5. Spain, D. M.: The Incidence of Multiple Primary Malignant Tumors and a Report of a Case With Three Primary Carcinomata, New York State J. Med. **49**: 1445-1447, 1949.
6. Tullis, J. L.: Multiple Primary Malignant Lesions, J. Lab. & Clin. Med. **27**: 588-594, 1942.
7. Warren, S., and Gates, O.: Multiple Primary Malignant Tumors. A Survey of the Literature and a Statistical Study, Am. J. Cancer **16**: 1358-1414, 1932.
8. Warren, S., and Ehrenreich, T.: Multiple Primary Malignant Tumors and Susceptibility to Cancer, Cancer Research **4**: 554-570, 1944.

(See discussion on page 358.)

THE SURGICAL MANAGEMENT OF CARCINOMA OF THE LUNG

A Study of the Cases Treated at the Massachusetts General Hospital from 1930 to 1950

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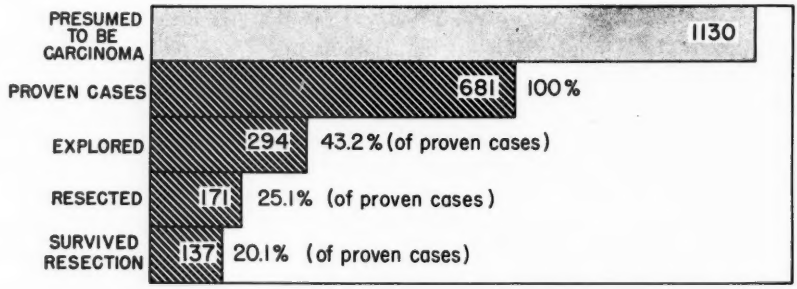
DURING the twenty-year period, 1930 to 1950, a clinical diagnosis of carcinoma of the lung was made in 1,130 patients at the Massachusetts General Hospital. In 681 of these, the presumptive diagnosis was confirmed by histologic evidence obtained by study of the surgical specimen, autopsy, or by biopsy of the original tumor or its metastases. Sarcoma, metastatic carcinoma, and other tumors of the lung have been excluded from the present study. Of these 681 proved cases, 294 patients were subjected to thoracotomy (Fig. 1) and a lobectomy or pneumonectomy carried out in 171 (25.1 per cent of proved cases, 58.2 per cent of those explored). One hundred and thirty-seven survived resection and left the hospital alive, 20.1 per cent of the patients in whom the diagnosis was established histologically. In order to avoid diagnostic error which could affect survival figures, the microscopic sections of the resected tumors have been reviewed with a pathologist and tumors of uncertain origin or cell characteristics excluded. Adenoma of the bronchus has been recognized as a separate entity and has not been included in the figures presented above. This has been done because, regardless of any controversy concerning its cell characteristics, its clinical behavior is such as to warrant separate consideration particularly in the light of survival rates after resection.

The patients who form the basis of this report include all those admitted to the medical and surgical services of the general hospital in whom the diagnosis was made, as well as those individuals referred to the private divisions of the hospital. In the majority, the diagnosis had not been established prior to admission. In histology, age, and sex distribution, they conform to the pattern of the disease that has been previously recorded in the literature. The follow-up on all who underwent resection before January, 1948—that is, at least two years prior to this study—is complete. Thus all figures relating to survival are based on a 100 per cent follow-up—a matter of basic importance in cancer statistics. The number of operations and hospital mortality for the years 1948 and 1949 have been added to round out the over-all picture for the twenty-year period. The patients treated in those two years have not been considered in the calculations of survival, but are inserted to characterize the present management of carcinoma of the lung better than the series extending back to 1930.

Read before the Thirtieth Annual Meeting of The American Association for Thoracic Surgery, Denver, Colo., April 15-18, 1950.

SELECTION OF OPERATION

In the twenty-year period, 1930 to 1950, 114 pneumonectomies and 57 lobectomies were performed for primary carcinoma of the lung. These operations were carried out on the basis of one of two fundamental assumptions. The first was that the disease was a localized process and therefore might be eradicated by surgical extirpation; the second, that the removal of a whole lung or one of its lobes might alleviate the suffering arising from pain, hemorrhage, or suppuration in uncontrollable cancer and thus make a limited period of survival more worth while.



PRIMARY CARCINOMA OF THE LUNG OVER A 20 YEAR PERIOD
1930 to 1950

Fig. 1.

Both operative mortality and survival rates have been calculated for the entire series without the usual attempt to correct for those resections undertaken when it may have been the estimate of the operator that the disease had exended beyond the limits of extirpation. In this as in all series of operations for cancer, many patients have been benefited even though they have ultimately died of the disease. It may be assumed, however, that resections undertaken for "palliation" only were evenly distributed between the lobectomy and pneumonectomy groups.

When resection is carried out under the first assumption, however, with full hope of eradicating what is believed to be a localized disease, the important question is whether significantly better results can be achieved if the entire organ is removed. The survival figures shown throw some light on this point. It should be understood that lobectomy has been carried out not merely as a local excision of a primary growth, but as a complete dissection of an anatomic unit of the lung to include the adjacent lymph nodes. There can be no difference of opinion as to the type of operation to be performed under circumstances that require a pneumonectomy for complete excision of a primary growth or grossly identified secondary deposits.

Lobectomy, with removal of all gross evidence of the disease, has been considered reasonable under the following conditions: (1) when there was evidence of diminished pulmonary or cardiac reserve; (2) when uncertainty

of diagnosis existed and the lesion in question could be totally excised by lobectomy; (3) when the lesion was small, peripheral, and without evidence of lymph node extension; (4) when the carcinoma had extended beyond surgical bounds, but when the bulk of primary tumor could be removed by lobectomy with the hope of relieving symptoms.

The patient's pulmonary reserve has been appraised upon clinical grounds rather than upon formal pulmonary "function" tests. Emphysema, pulmonary fibrosis, previous pulmonary disease, and old injuries to the chest wall have been taken into account and ability to perform the usual daily tasks without unusual dyspnea taken as the measure of exercise tolerance. The apparent rather than the actual age of the patient has been a part of our estimate of pulmonary reserve. Diminished cardiac reserve has been assumed if there was a history of congestive failure, angina pectoris, hypertension, or arteriosclerosis, especially when supported by evidence of coronary insufficiency or past myocardial infarcation in the electrocardiogram or by cardiac enlargement and tortuosity of the great vessels in the roentgenographic examination of the chest.

Uncertainty of diagnosis has led to the employment of lobectomy as a means of establishing the presence of malignant disease before accepting the commitment to total pneumonectomy. If the diagnosis of cancer was confirmed and the resected lymph nodes proved uninvolved, the question then arose as to the need to extend a lobectomy to a pneumonectomy. At this point the operator has been guided by what in his judgment constituted a reasonable effort to eradicate the disease by extirpation balanced against the status of the patient, particularly with respect to his cardiorespiratory function. Lobectomy is not merely a local resection of the primary growth. As performed in our hands it has included not only the lymph nodes at the level of the lobar bronchus, but also mediastinal nodes. For example, a right upper lobectomy should include the division of the azygos vein and removal of the paratracheal nodes as well as those lying superior to the right pulmonary artery anterior to the trachea. It has sometimes included resection of the right middle lobe with resection of the nodes lying below the middle lobe bronchus.

Small peripheral tumors with grossly negative lymph nodes have often been treated by lobectomy. The increasing frequency of these tumors that results from earlier diagnosis of the disease introduces a very serious question as to whether wide excision of apparently normal lung tissue is as vital to the life of the patient as the maximum preservation of his pulmonary reserve.

Last, some lobectomies have been performed for severe hemorrhage, pain secondary to chest wall invasion, or localized infection arising from a tumor primary in that lobe, even though there were widespread metastases.

In each patient the decision as to the type of resection has been based upon a number of considerations that apply to the individual concerned rather than upon arbitrary rules drawn up without regard to their applicability to the problem at hand.

With this statement of general policy in the management of cancer of the lung, we present the results of pneumonectomy and lobectomy at the Massachusetts General Hospital from 1930 to the present.

OPERATIVE MORTALITY

Among 294 patients who were explored, 171 (58.2 per cent) had resections (25.1 per cent of all proved cases). The first lobectomy for carcinoma in this series was performed in 1930,* the first pneumonectomy in 1933.† Among those who had exploratory thoracotomies only, the mortality was 10.6 per cent. Of 114 patients who underwent pneumonectomy, there were 26 hospital deaths in the years 1933 to 1950, an operative mortality of 22.8 per cent. Of 57 patients treated by lobectomy from 1930 to 1950, there were 8 deaths, an operative mortality of 14 per cent (Fig. 2). Although this means a higher hospital survival rate for the smaller series of cases treated by lobectomy, it should be noted that many of the patients who died following pneumonectomy could not have had complete extirpation of their disease by less radical surgery so that the procedure was indicated in the face of added risk. The ages of the patients who had pneumonectomies are much the same as those who had lobectomies, both as to average age and maximum age. These figures have been plotted in Fig. 3.

The operative mortality rates computed for a series extending back to 1930 are chiefly of historical interest. A more accurate picture of the immediate status of pulmonary resection for cancer is given by our experience in the years 1948 and 1949. In these years was felt the full effect of present-day measures to combat infection, replace blood loss, and deal with cardio-respiratory problems, but, more important, the encouraging evidence that these patients were coming to surgery earlier in their disease. For comparison, therefore, in Fig. 2 the mortality rates are divided into resections performed before 1948 and those performed in 1948 and 1949. Among 87 pneumonectomies in the years 1933 through 1947 there were 25 deaths, an operative mortality of 28.7 per cent compared with one death following 27 pneumonectomies in 1948 and 1949, an operative mortality of 3.7 per cent. After 31 lobectomies in the years 1930 through 1947, there were 7 deaths, an operative mortality of 22.6 per cent compared with 1 death following lobectomy in 26 patients in the years 1948 and 1949, an operative mortality of 3.8 per cent. The equality of distribution between the two types of resection in 1948 and 1949 is worthy of note.

*The lobectomies in this series include the early cases reported in 1933 (J. THORACIC SURG. 2: 254). In the first lobectomy performed on Oct. 30, 1930, the carcinoma was too close to the hilum to permit the use of the tourniquet technique then in common usage. Individual ligation of the lobar artery and vein was followed by transection of the lobar bronchus. Because Sauerbruch had reported several deaths from mediastinal emphysema following primary closure of a large bronchus at the hilum, a tube was sutured to the bronchial stump and brought to the outside of the chest wall. The patient died of pneumonia.

The patient recorded as Case 4 in the above-mentioned article is still living. Her tumor was later classified as an adenoma. The lower and middle lobes were removed on Aug. 10, 1931, by intrahilar dissection and the intermediate bronchus closed by primary suture.

†The first pneumonectomy of this series was a single stage resection of the right lung and a portion of the diaphragm for adenocarcinoma performed on Nov. 9, 1933. The patient (M.G.H., No. 332942) was discharged ambulatory on December 9 and returned to her home. She was readmitted on December 15 and died on Dec. 24, 1933. Autopsy showed sound healing of the operation site but widely disseminated metastic carcinoma.

In Overholt's case (J. THORACIC SURG. 4: 196, 1934), repeatedly referred to as the "first single stage right pneumonectomy," the date of operation is recorded as 11 days after November 2 (Nov. 13, 1933). The patient is reported as surviving and it has been stated that the tumor was subsequently reclassified as bronchial adenoma.

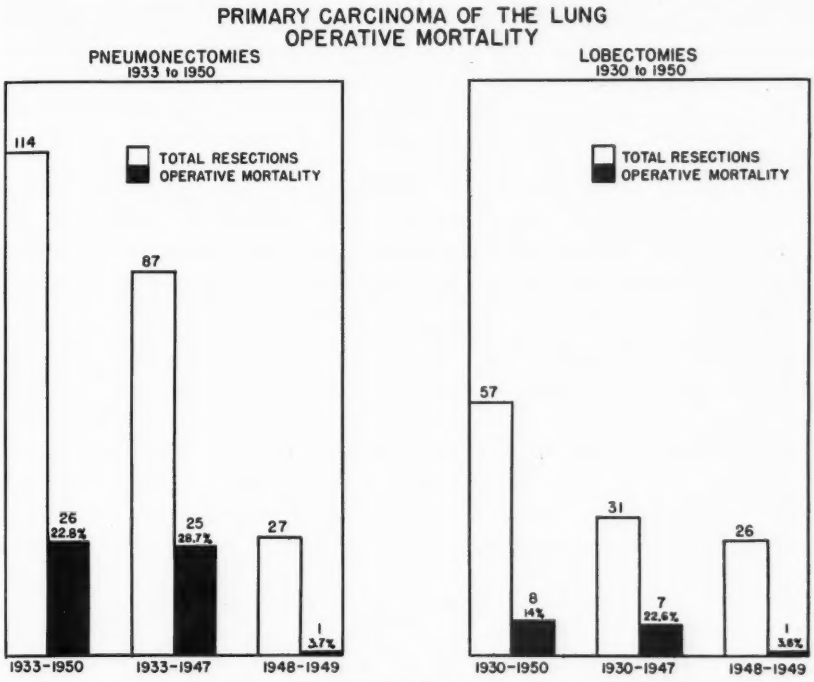

PRIMARY CARCINOMA OF THE LUNG
OPERATIVE MORTALITY
PNEUMONECTOMIES
1933 to 1950
LOBECTOMIES
1930 to 1950
TOTAL RESECTIONS
OPERATIVE MORTALITY
114
26
22.8%
87
25
28.7%
27
1
3.7%
57
8
14%
31
7
22.6%
26
1
3.8%
1933-1950
1933-1947
1948-1949
1930-1950
1930-1947
1948-1949

Fig. 2.

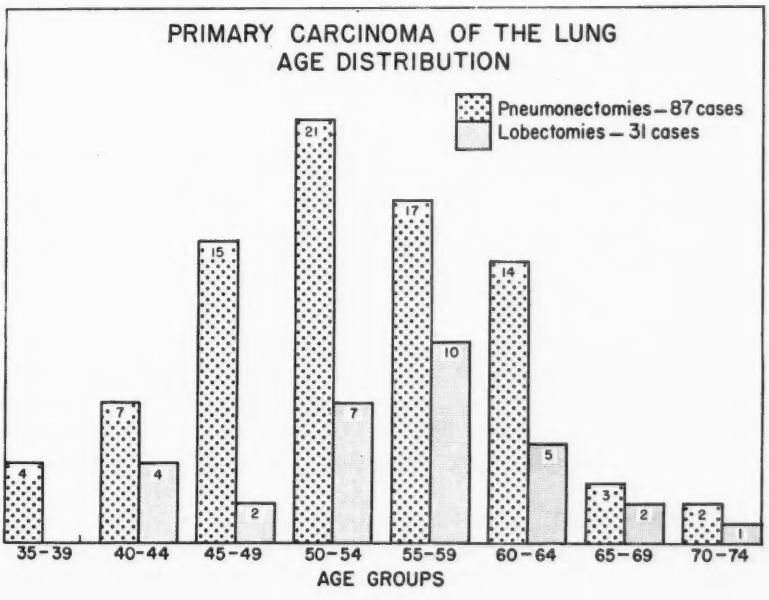

PRIMARY CARCINOMA OF THE LUNG
AGE DISTRIBUTION
Pneumonectomies – 87 cases
Lobectomies – 31 cases
4
7
4
15
2
21
7
17
10
14
5
3
2
2
1
35-39
40-44
45-49
50-54
55-59
60-64
65-69
70-74
AGE GROUPS

Fig. 3.

The effect of chest surveys in adding early tumors among favorable subjects for surgery is important. The increasing awareness of doctors and patients alike to the necessity for chest x-ray examinations followed by diagnostic studies for abnormal lung shadows has enabled more patients to be operated upon while their tumors were still in a stage amenable to resection.

SURVIVAL

The survival rates for patients treated by resection is presented in the following ways: (1) percentage of five-year survival among patients operated upon five or more years ago; (2) percentage survival by six-month periods up to five years of all patients who underwent resection. The number of patients entering into this calculation diminishes, of course, after three years as those cases done less than three to five years before are excluded; (3) percentage survival also by six-month periods up to five years of patients who left the

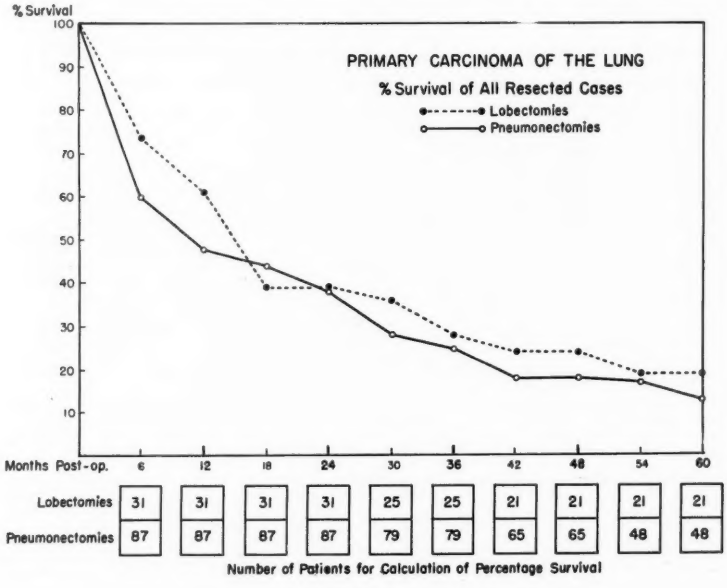


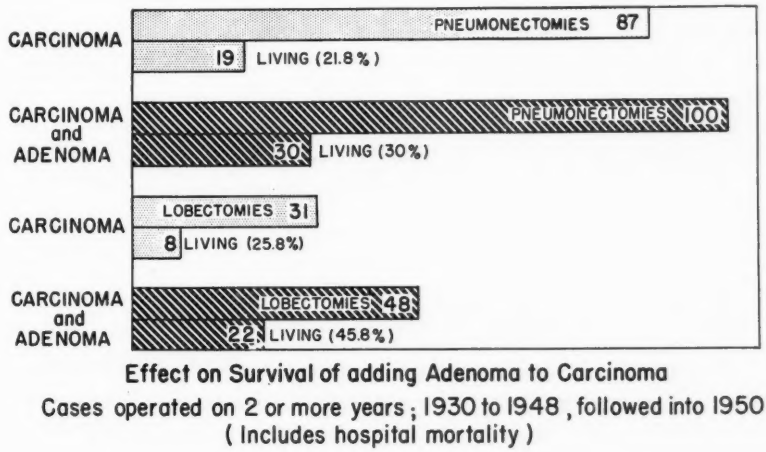
Fig. 4.

hospital alive after operation; (4) percentage survival by six-month intervals of all patients who underwent resection, either lobectomy or pneumonectomy, classified according to the presence or absence of lymph node involvement noted in pathologic examination of the resected specimen; and finally (5) the number of patients at present surviving among all individuals who have undergone resection.

There were 48 patients who had a pneumonectomy five or more years ago and of these, 6, or 12 per cent, survived five or more years. Similarly, there were 21 patients treated by lobectomy five or more years ago, 4, or 19 per cent, survived five or more years (Fig. 4).

It is instructive to add the 17 lobectomies and 13 pneumonectomies that were done for adenoma to the group of patients in whom these procedures were carried out for carcinoma. Among the patients with adenoma, there were two hospital deaths, none later than 1936. There were 3 patients who died a year or more after leaving the hospital, all 3 of other diseases, none of whom had evidence of recurrence or distant metastases at autopsy. Added to the carcinomas they make a total of 100 pneumonectomies and 48 lobectomies performed before 1948. The two-year survival rates, including hospital mortality, are charted in Fig. 5. They raise the survival for all cases followed at least two years for pneumonectomy from 22 to 30 per cent and for lobectomy from 26 to 46 per cent.

Returning to the problem of carcinoma of the lung exclusive of adenoma, if one considers percentage survival by six-month periods up to five years, the curves for lobectomies and pneumonectomies are also in close agreement, either according to patients who left the hospital and therefore had an opportunity to survive, or according to the total number of patients undergoing resection. Among the latter, the increased hospital mortality in the pneumonectomy group during the period 1930 to 1947 increases slightly the margin in favor of lobectomy.



Effect on Survival of adding Adenoma to Carcinoma
Cases operated on 2 or more years; 1930 to 1948, followed into 1950
(Includes hospital mortality)

Fig. 5.

The rate of survival for those who left the hospital alive after resection for primary carcinoma has been charted in Fig. 6. It shows a five-year survival rate of 20 per cent for the pneumonectomies (6 patients surviving five or more years), and a 25 per cent for lobectomies (4 patients surviving five or more years).

As might be predicted, the presence of involved lymph nodes in the operative specimen decreased the long term chances of survival of the patients who left the hospital alive. These figures are graphically presented in Fig. 7. Of 29 patients with negative nodes, 10, or 34 per cent, survived five years, and

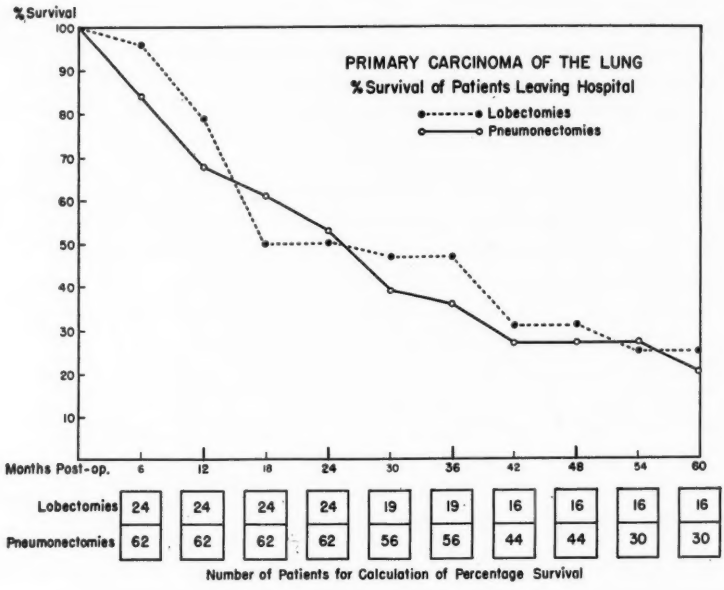

% Survival
PRIMARY CARCINOMA OF THE LUNG
% Survival of Patients Leaving Hospital
Lobectomies
Pneumonectomies
Months Post-op.
Number of Patients for Calculation of Percentage Survival

Fig. 6.

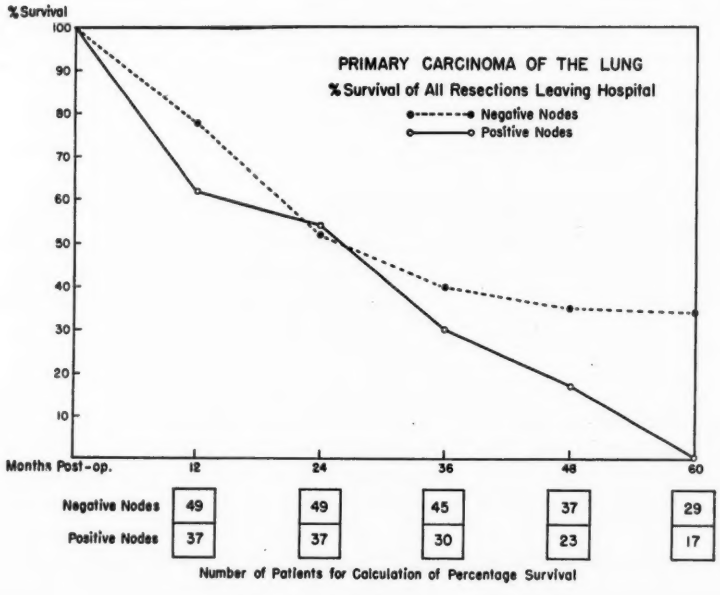

% Survival
PRIMARY CARCINOMA OF THE LUNG
% Survival of All Resections Leaving Hospital
Negative Nodes
Positive Nodes
Months Post-op.
Number of Patients for Calculation of Percentage Survival

Fig. 7.

there was no survivor at five years among those with positive nodes. Only patients operated upon five or more years ago are considered. Of the patients operated upon within five years there are 2 with positive nodes who are still alive more than four years after operation.

Considering the survival of patients on an individual basis, 4 of the patients who had pneumonectomies are alive and well over six years after operation. Four of those who had lobectomies are alive and well seven years or more postoperatively, 1 having survived for fourteen years. Among those who survived pneumonectomy there are 3 who died at four and one-half, seven and one-half, and ten and one-half years, respectively. One died at four and one-half years of carcinoma of the stomach, and the other two presumably of recurrence of their disease. One patient died four years after lobectomy and at autopsy no evidence of recurrent disease was found.

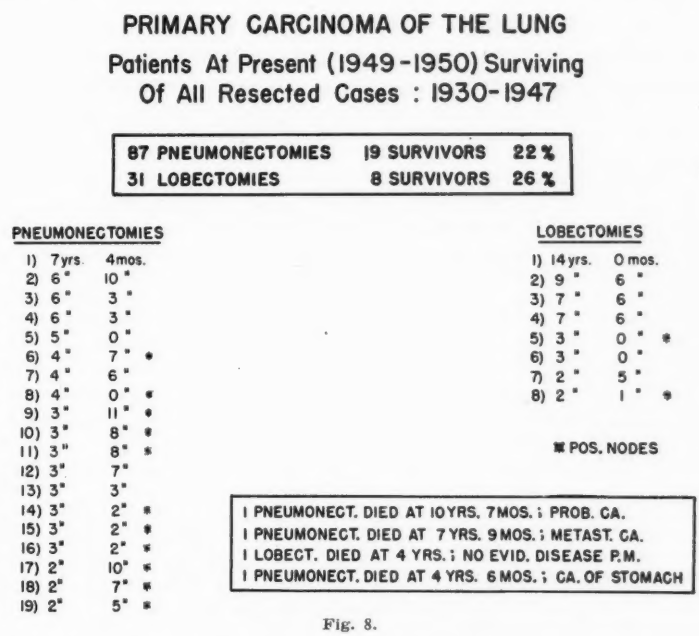

PRIMARY CARCINOMA OF THE LUNG
Patients At Present (1949-1950) Surviving
Of All Resected Cases : 1930-1947
87 PNEUMONECTOMIES 19 SURVIVORS 22 %
31 LOBECTOMIES 8 SURVIVORS 26 %
PNEUMONECTOMIES
1) 7yrs. 4mos.
2) 6 " 10 "
3) 6 " 3 "
4) 6 " 3 "
5) 5 " 0 "
6) 4 " 7 " *
7) 4 " 6 "
8) 4 " 0 " *
9) 3 " 11 " *
10) 3 " 8 " *
11) 3 " 8 " *
12) 3 " 7 "
13) 3 " 3 "
14) 3 " 2 " *
15) 3 " 2 " *
16) 3 " 2 " *
17) 2 " 10 " *
18) 2 " 7 " *
19) 2 " 5 " *
LOBECTOMIES
1) 14 yrs. 0 mos.
2) 9 " 6 "
3) 7 " 6 "
4) 7 " 6 "
5) 3 " 0 " *
6) 3 " 0 "
7) 2 " 5 "
8) 2 " 1 " *
* POS. NODES
1 PNEUMONECT. DIED AT 10 YRS. 7 MOS.; PROB. CA.
1 PNEUMONECT. DIED AT 7 YRS. 9 MOS.; METAST. CA.
1 LOBECT. DIED AT 4 YRS.; NO EVID. DISEASE P.M.
1 PNEUMONECT. DIED AT 4 YRS. 6 MOS.; CA. OF STOMACH

Fig. 8.

At the present time, of the 87 patients who underwent total pneumonectomy before 1948, 19, or 22 per cent, survive. Of the 31 patients who underwent lobectomy in the same period, 8, or 26 per cent, are now alive, and so far as we are aware, free of disease (Fig. 8).

SUMMARY

1. The total experience with proved cases of primary carcinoma of the lung at the Massachusetts General Hospital for the twenty-year period, 1930 to 1950, has been presented.

2. The conditions under which lobectomy has been carried out in the treatment of cancer of the lung are reviewed.

3. Operative mortality statistics for lobectomy and pneumonectomy for the twenty-year period and for the last two years separately have been noted. In the past two years the operative mortality for both pneumonectomy and lobectomy has been less than 4 per cent.

4. The follow-up on the 87 pneumonectomies and 31 lobectomies performed before 1948 is complete. There is remarkably close agreement in survival rates for the two procedures.

5. As might be predicted, the presence of involved lymph nodes in the resected specimen has greatly diminished the patient's chance of long-term survival.

DISCUSSION ON "MULTIPLE CANCERS: PRIMARY IN THE LUNG AND OTHER SITES" BY DR. WILLIAM G. CAHAN, DR. FRANK S. BUTLER, DR. WILLIAM L. WATSON, AND DR. JOHN L. POOL;* AND "THE SURGICAL MANAGEMENT OF CARCINOMA OF THE LUNG" BY DR. EDWARD D. CHURCHILL, DR. RICHARD H. SWEET, DR. LAMAR SOUTTER, AND DR. J. GORDON SCANNELL

DR. ARTHUR H. AUFSES, New York.—It is interesting to hear Dr. Cahan and his associates present the results of their resection therapy in carcinoma of the lung, including a large number of lobectomies. When Dr. Harold Neuhof and I presented a paper before this Association in 1947, suggesting that lobectomy might be an adequate operation in certain types of carcinoma of the lung, it aroused considerable discussion, most of which was adverse. For that reason I should like to show two slides, one of which shows the results at Mt. Sinai Hospital in patients who survived operation over a period of 13 years from 1935 to 1947, inclusive.

(Slide.) Eighty-six patients survived operation; of the 86, 52 had pneumonectomies and 34 lobectomies. At the present date, 17 patients who had pneumonectomy are alive and well or considered cured, and 13 who had lobectomy, alive and well or considered cured. By cured, we mean that a few have since died but we have post-mortem evidence that they died of coronary or other diseases four or more years after operation, and at post mortem no evidence of the original carcinoma was found in the body. No patient who died within four years of operation is included in this group as considered cured. As you see, of 34 lobectomies, 13 are alive and well, 38 per cent. In the early years that we performed this operation there were four patients upon whom we performed lobectomies who would not meet our criteria today; if they were omitted from this series the percentage of survivals would be 43 per cent. Incidentally, of the 17 pneumonectomies, 7 are alive after more than five years, and, of the 13 lobectomies, 8 are alive for more than five years. So that we have a rather high percentage of lobectomies alive in comparison with the pneumonectomies. We believe that the patients with lobectomy will hold up.

(Slide.) We reviewed 849 carcinomas of the lung seen at Mt. Sinai Hospital over the same thirteen-year period and grouped them according to the length of time that they had symptoms—one month, two months, three months, four to six months, seven to twelve months, one to two years, and longer. If we take the survival rate in the various "duration of symptoms periods," we see that in the one-, two- and three-month periods the survival rate is only 2.8 per cent; in the six-month period it is 3.5 per cent; and in the one-year period 3.9 per cent. If we take the cases who had a longer history, more than one year, we have the remarkable figure of 3.9 per cent survival rate, which would seem to indicate

*See page 335 for article by Cahan, Butler, Watson, and Pool.

that there are really two types of tumors: (1) the slow-growing type, the type one sees on the x-ray on routine examination, without symptoms, a small peripheral tumor. We feel that if no involved lymph nodes are found at operation, this type is a subject for lobectomy. (2) The main bronchus, rapid-growing and spreading lesion which gives early symptoms.

DR. T. R. HUDSON, Chicago.—At Hines Veterans Administration Hospital and Wesley Memorial Hospital in Chicago we are currently engaged in a study of 150 cases of patients subjected to surgical treatment for carcinoma of the lung. The study is incomplete but at present we have been able to follow and have statistics on 114; 83 of those patients had pneumonectomy and, of the 83, 15 are alive today, an 18 per cent survival rate. Thirty-one patients had lobectomy and, of the 31, 8 are alive today—25 per cent survival. The earliest lobectomy was done 18 months ago and the oldest one 13 years ago, in 1937. This patient had a right lower lobe removed, also a number of ribs and a portion of the diaphragm because of local invasion. The mortality figures on the lobectomy are one death in 31 cases; for the pneumonectomies the figure was 4.5 per cent. That does not include any cases prior to 1943.

DR. EVARTS A. GRAHAM, St. Louis.—I am sure everyone has enjoyed these two interesting and important papers on this very important subject of bronchiogenic carcinoma. It seems to me that the results given by Dr. Soutter, from Dr. Churchill's and Dr. Sweet's clinic, show conclusively that patients will survive a five-year period after lobectomy in some instances. I think, however, that we should distinguish between what might be considered the ideal operation for cancer—and cancer is about the same whether in the lung or elsewhere—and one which theoretically is not ideal but will sometimes work. The statistics reported today are, I would say, of no significance except that they indicate that some patients will survive a five-year period after lobectomy. One cannot draw any conclusions from a small number of cases, less than several thousand, I would say, about which operation is the best so far as giving a high percentage of five-year survival rates. I think we are likely to be misled, perhaps, by the presentation of statistics which, because of the small number, do not really have much significance. There are not available at the present time a sufficiently large number of patients who have been operated upon for bronchiogenic carcinoma, to have statistically significant figures on end results.

I am glad, however, to have this subject brought up. There is no doubt, as everyone who has had experience in dealing with this disease realizes full well, that there are cases in which it is worth while to take a chance on a lobectomy because of the horrible situation in which the patient may be left if total pneumonectomy is performed. After all, a bad respiratory cripple is a very pathetic figure, and it is questionable whether we have done an act of kindness to some of those people by permitting them to live for more than five years, we will say, in this pathetic condition. It might be far better to take a chance with lobectomy in such a case and make the patient less of a respiratory cripple than he would be by perhaps doing a better theoretical operation—a total pneumonectomy—but leaving him so uncomfortable that life is hardly worth while for him.

I am rather surprised, in the series just quoted from Boston, that they have no successful results in cases with involved glands. In a series we studied of more than five-year survivals prior to 1947, we had three patients who had survived more than five years who had had involved glands. As a matter of fact, the Pittsburgh doctor who was my first patient for pneumonectomy showed, when his lung was re-examined many years later, that he had two involved glands invaded by carcinoma. He has passed his seventeenth year and is now in his eighteenth year, well, and still practicing obstetrics. We have had two other patients with involved glands who have survived more than five years.

There is one other point on which I want to "stick out my neck;" if there are any pathologists here perhaps they would like to say something on this to put me in my proper place. That is—and I just venture to put this proposition to you—that I think that before many more years have passed, you will all agree that many times the so-called adenocar-

cinoma arises in what is sometimes spoken of as the bronchial adenoma. Therefore, when one makes rigid distinctions in saying that he is dealing with and discussing adenocarcinoma, but is not saying anything at all about adenoma, I think he is making a mistake.

DR. M. E. DE BAKEY, Houston.—It is gratifying to observe the rather good results obtained by Dr. Churchill and his associates following lobectomy in carcinoma of the lung. I would add, however, that I am not particularly surprised at these results, because the mere fact that a lobectomy was done in these patients is, I think, a selective factor which tends to screen out the more advanced case. We know that there are a number of factors that affect the survival rate following resection in carcinoma of the lung. We have attempted to ascertain some of these factors by an analysis of our experience. On the basis of this analysis it was found that the most significant of all factors affecting prognosis is whether or not the lesion is still confined to the lung. The fact that lobectomy could be done in the cases just presented is an indication that the lesion was still localized within the lobe, and consequently had not extended beyond the borders of the lung. There is, of course, the possibility that in a certain number of the cases the disease may have extended by way of the lymphatics to the mediastinal nodes which may not have been reached by lobectomy, but certainly a fair proportion of the total number of patients in whom lobectomy was done would be those in which there was no extrapulmonary extension of the lesion. The significance of this factor, that is, the status of the growth at the time of operation, is well demonstrated in our pneumonectomy series by analysis of the cases into two groups; first, those in which the lesion was still confined to the lung and, second, those in which the lesion had already extended beyond the borders of the lung, either by extension of the disease grossly to the adjacent structures or to the regional lymph nodes. The difference in the five-year survival rates between these two groups was quite significant, the figures being respectively about 40 per cent and 12.5 per cent.

It is my impression that the purpose of this study by Dr. Churchill and his associates is not to determine whether lobectomy or pneumonectomy is the procedure of choice in carcinoma of the lung, but rather to learn if lobectomy under certain conditions would provide equally satisfactory results. Certainly, this is highly desirable information. As Dr. Graham has said, most of us have had experience with patients in whom we have felt that lobectomy might be a less risky and, under the circumstances, the preferable procedure. This presentation provides additional support for that belief. The indications given by Dr. Soutter showed that they have used this procedure, not as the procedure of choice for all cases of carcinoma of the lung, but rather as the procedure of choice in a given set of circumstances. I think this is an important point to keep in mind.

Finally, I would like to merely mention the fact, in support again of what Dr. Graham has said about not drawing definitive conclusions from statistics of this kind, that there are a number of factors in addition to the status of the growth which I have already mentioned that can influence the results in any given series, particularly in a relatively small series. I do not think we have yet acquired sufficiently large series to permit disregard of these variables in the statistical analysis. For example, the results can be greatly influenced by the number of private cases and the number of charity cases in the series. In our experience, the resectability rate was some three or four times greater among private cases than among the charity cases; this simply means that the former type of patient will have the less advanced and more likely curable lesion. Still another factor is the histologic type and grade of the growth. Thus it has been found that the most favorable survival rate occurred in patients with epidermoid carcinoma, and the poorest in those with undifferentiated carcinoma, and in both forms there was a progressive rise in fatality rates from Grade I to Grade IV. It is thus apparent that these and other variables and their relative weight in any series of cases may have an important bearing upon the results of an analysis.

DR. ARTHUR H. AUFSES, New York.—As you know, Dr. Neuhof and I have been attempting to make a survey among the members of this Association with regard to their results in resection for carcinoma of the lung, and we have sent out questionnaires and

asked for a follow-up on patients who were alive and well six months or more after operation; in other words, we did not want to make the task too difficult; we felt that in that way we would eliminate those patients upon whom operation had not materially affected the course of the disease.

We have received replies on 470 patients. I would like to show the results because it adds up to a greater number of patients than any one clinic or surgeon can collect, and the results are quite germane to the present discussion. (slide.) In the 470 patients alive and well six months after operation, 123 were living and well two years or more after operation; 94 had pneumonectomies, 29 had lobectomies. There were 145 who developed recurrence or died within two years after operation, that is, between six months and twenty-four months. Then there is the question whether a two-year or thirty-month follow-up was a good follow-up period; 36 of the group of 470 patients developed recurrence or died after two years. Dividing them with respect to pnuemonectomy and lobectomy, the great majority fell by the wayside in the third year, a scattering in the fourth year, one in the fifth year, and three in the sixth year.

A group of 164 patients were alive and well less than two years after operation; of course that is an indeterminate group—we do not know which way they will go.

(Slide.) In 123 patients living and well more than two years after operation, we have classified them as to duration of survival; of 94 pneumonectomies, 29 are alive for more than five years; of 29 who had lobectomies, eight are alive more than five years following operation.

(Slide.) We were most interested in the question of node involvement. Of the 123 patients, there were no involved nodes at operation in 92, or 75 per cent; there were hilar nodes involved in 22, or 18 per cent. As you see, the duration of survival of these 22 patients indicates that at least 6 are alive over the five-year period. Of 9 patients with mediastinal and hilar node involvement (7 per cent) only 1 is alive over the five-year period, and 3 in the four- to five-year period. Then there are 145 patients who died or had recurrence from six months to two years after operation—45 per cent of whom had no node involvement at operation. Many died with metastases in distant parts of the body which is probably evidence of hematogenous spread.

We would like to go on with this survey, and we ask those men who have not sent in their questionnaires to please aid us, for we would like to accumulate a large series of cases.

DR. JOHN H. GIBBON, JR., Philadelphia.—I am very much interested in this subject. I feel as Dr. DeBakey does. When you see the slide shown by Dr. Soutter of five-year survivals, and see that there is relatively little difference between lobectomies and pneumonectomies, you might be misled to think that the authors of the paper believe that lobectomy is just as good an operation as pneumonectomy for cancer of the lung. Obviously, as Dr. DeBakey said, lobectomies can be performed only when the lesion is confined to the peripheral portions of the lung. What we are all interested in when dealing with cancer of any organ is the number of patients who survive five years in proportion to the entire number seen who have proved cancer of that organ. If, by performing a lesser operation such as lobectomy in certain selected cases where the lesion is confined to the parenchyma of the lung, one can reduce the operative mortality significantly, then perhaps one can increase the total five-year salvage rate of all the patients seen with the disease. It seems to me that is the important lesson to be learned from this series. I believe that in several of the large series of carcinoma of the lung that have been reported, 5 to 8 per cent of the entire number have survived five years. We have a small series of 276 cases of carcinoma of the lung seen in the last four years, and we can speak only of the three-year survival rate. It is in the neighborhood of 11 per cent of all the patients seen. We have performed 114 resections for cancer of the lung; all but four were pneumonectomies. Our mortality rate is 22 per cent. If we could cut that mortality rate by doing lobectomies in special types of cases, such as the authors of this paper have outlined, perhaps we could increase our total salvage rate.

DR. ALTON OCHSNER, New Orleans.—This is not the same individual making two discussions although it is the same team—I will admit that and I apologize.

Although Dr. Churchill and his associates would not want to give the impression, I fear that this discussion may do a great deal of harm, just as the discussion which is rampant at the present time in most surgical organizations as to whether one should do an anterior resection for low-lying lesions in rectal carcinomas. It is true that one can get by with them in many instances, but as Dr. Graham has emphasized, we are interested in curing patients. Everyone has emphasized this morning the desirability of doing pneumonectomy if the lesion is not limited to the lobe. Unfortunately, at the time of operation one cannot tell if the lesion is limited, and it is only after the lung is out and careful examination of the mediastinal nodes has been done that one knows whether there has been extension to these nodes. For this reason I feel that lobectomy should be limited to those cases in which pneumonectomy is contraindicated, not those in which lobectomy can be done; but if, for reasons such as a bad cardiovascular system, or if the differential study of pulmonary function would indicate that the patient could not get along with one lung, then one should do a lobectomy, and only then.

In our series of 237 cases, only 5 had lobectomies; of the 5, 3 are dead with carcinoma, 1 is living with carcinoma, and 1 apparently has no carcinoma. I would like to request that when people report statistics, that the statistics give all the cases operated upon and not only those that survive operation. Because that immediately dilutes the statistics. Why not say that these results are based upon those patients that have survived five years? That of those that survived five years, a certain percentage are still alive. Unless we include all the cases and do not consider only those that survive operation, there is dilution of statistics, which does not mean a great deal.

DR. JOHN W. STRIEDER, Brookline, Mass.—In connection with the stimulating paper of Dr. Cahan and his group at Memorial Hospital, I would like briefly to recount an experience which has seemed to us of some interest and significance. During the past year we have seen three women, each of whom had had a breast removed for cancer from two to six years prior to the time they were seen by us. Two of the patients had been followed by x-ray very faithfully; one had never had an x-ray either prior to her mastectomy or for two years subsequently. All these patients at the time they were seen by us showed pulmonary tumors which were suspicious of metastatic disease and all were explored. One proved to have an inoperable bronchiogenic carcinoma; the other two had bronchial adenomas for which restrictions could be done.

This also raises the question of what to do, in view of the known propensity of carcinoma of the breast to have multiple metastases, if shadows are present in the chest x-ray at the time the diagnosis of carcinoma of the breast is made. As Dr. Cahan has suggested, it would seem that we should have no hesitation, if there is no demonstration of multiple sites, to explore these patients at a suitable time.

MR. P. R. ALLISON, Leeds, England.—I was about three miles off the coast of America when I heard a sort of Indian war cry to the effect that Churchill was doing lobectomies for bronchial carcinoma. Anybody who has listened carefully to this most clear and precise paper presented by the Boston school today must agree that they are in fact still recommending pneumonectomy for carcinoma, and that their choice of patients for lobectomy is both reasonable and logical. I think it would be a good thing if, at the end of the discussion, they emphasized their confidence in pneumonectomy as a desirable treatment for most patients.

It is difficult to assess the importance of the two forms of treatment when they are used for different sorts of patients and different types of disease. We must also remember that the results of treatment for the last fifteen years are influenced by various cross currents. We have the antibiotics, which have had a profound influence, safe transfusions, improved anesthesia and improved technique. The effect of these lines of progress is shown in my own series, for of 101 radical pneumonectomies performed for carcinoma between 1940 and 1949, the total operative mortality was 23 per cent, but in 1948 it was only 12

per cent, and in 1949 it was 4 per cent. In the early years, trouble with the bronchial stump, producing fistula, empyema, and all its complications, turned the scale against many poor risk patients, but in the last three years the performance of 63 radical pneumonectomies for bronchial carcinoma in my unit has been associated with only one bronchial fistula. Other factors which are pertinent to this discussion are the education of the physician and the increasing use of mass radiography, which bring more early lesions to the notice of the surgeon. Of 1,050 patients with bronchial carcinoma seen between 1941 and 1948, the lung could be removed in only 7 per cent, whereas of 178 patients seen in 1949 this end could be achieved in 16 per cent.

Some further confusion in the assessment of results of lobectomy and pneumonectomy may occur from lack of definition of the terms. The description of the upper lobectomy, which Dr. Soutter has given, with dissection of the mediastinal glands, seems adequate, but pneumonectomy has not been defined. I have seen many excisions of the lung for carcinoma which, from the point of view of malignant disease, are in nowise superior to lobectomy. In these operations much good lung tissue is removed without a more radical attack on the malignant disease. We must remember that malignant cells pass through cellular tissue, lymphatic vessels, and into lymphatic glands, and that only when this is gross is it palpable. It is easy to feel in the mediastinum, find a few soft glands, and say to one's self that these are not involved, but we should remind ourselves that we need a microscope to decide this point. To do either a lobectomy or a pneumonectomy and then pick out isolated glands from the mediastinum is to forget our surgical pathology. I should like to introduce the term "radical pneumonectomy" as applied to malignant disease, and to emphasize that all tissues removed should be removed in continuity, as we do in other parts of the body. For many years now I have found it convenient to do such a radical pneumonectomy in continuity, by dividing the pulmonary vessels within the pericardium and removing the pericardium adjacent to the lung root with its mediastinal cellular tissue and glands attached.

In 1942, the proportion of extrapericardial and intrapericardial dissections in my clinic was six to one, but in 1948, of 22 patients operated upon, all were done by intrapericardial radical dissection in continuity, and in 1949, of 27 patients, 23 were treated in this way. At the same time as the operation has been more radical the mortality has been reduced from 23 to 4 per cent.

If circumstances such as those described by Dr. Soutter justify the performance of a lobectomy rather than a pneumonectomy, this also should be done with the most careful lymphatic dissection, but I cannot agree that the glands in the hilum of the lung can be dissected as carefully with a lobectomy as with a pneumonectomy.

DR. S. O. FREEDLANDER, Cleveland.—My remarks shall be confined to the choice of lobectomy for carcinoma in the poor risk patient, that is, those patients with emphysema and low respiratory reserve. It is assumed in those cases that the more lung that is left in, the better the respiratory function will be. There may be some doubt regarding this. If lobectomy is done when there is already an increased dead space due to emphysema, and that dead space is further increased by more distension of the lung, and then circulation continues in that lung, the patient will get a mixture of blood that is more poorly oxygenated than if the total lung were removed. Thus we may have more respiratory incapacity following lobectomy than following pneumonectomy in this type of patient.

DR. LEO ELOESSER, San Francisco.—It seems to me that once more the thoracic surgeons have said something of importance to general surgery. This paper of Dr. Churchill's is very important indeed; it isn't only lung cancer, but rectal cancer and breast cancer and other cancers that are involved. Perhaps by setting up rigid ideals we are doing something that is not entirely justifiable. Too often we are doing operations that are futile on the one hand and unnecessary on the other. The attempt to eradicate cancer by progressively increasing the anatomic limits of operation is not the right road to follow. We must have some regard to what happens to the man who is alive after operation. What Dr. Graham said, Shakespeare said in Coriolanus—"They that prefer a noble life before a long one . . ." I won't give the rest of that quotation because it might spoil its pertinence here.

DR. JEROME HEAD, Chicago.—Dr. Graham has just stated that the statistics presented by Dr. Churchill and his associates are of very little significance. I do not agree with this. Any statistics are of relative value, but at the present time these are the only statistics which we have and therefore are those upon which we must work. It was very interesting to me to note that in our series of bronchiogenic carcinomas, which have just been reported by Dr. Hudson, the results are almost identical with those of Dr. Churchill and his group; namely, a 25 per cent survival rate in lobectomies and 18 per cent survival rate in pneumonectomies. The only way in which we are going to solve this question is by continuing to select cases and continuing to do pneumonectomies and lobectomies where each operation is either necessary or seems indicated. I am sure that further statistics will show better results following lobectomy, not because lobectomy is necessarily a better operation for carcinoma of the bronchus, but because of the type of case which is amenable to lobectomy. It is our practice at the present time to remove the lung where it is at all feasible. If it is necessary to open the pericardium and ligate the vessels within the pericardium, we do this. If it is necessary to remove a section of the esophagus into which the tumor has grown, we do this. After we have removed the lung, we dissect out the glands from the mediastinum. In all of these cases, in which the tumor is in a main bronchus close to the hilus, pneumonectomy is obligatory. Certainly many of the operations must be considered as palliative and certainly in a very high percentage of them all of the tumor is not removed. The cases in which lobectomy is feasible are the favorable cases. In these the hilus is not appreciably involved and one can make a relatively clean dissection. I am convinced that the lymph glands at the hilus of the lung can be removed by lobectomy as well as by pneumonectomy, and certainly the mediastinum can be dissected as well following lobectomy as following pneumonectomy. One must consider that in the individuals in the age group in which carcinoma of the bronchus most often occurs, pneumonectomy is definitely a crippling operation, whereas lobectomy is well tolerated and leaves the patient with almost normal respiratory function. For this reason I believe that lobectomy is preferable where it is feasible, even though it entails a slightly greater risk of recurrence. Personally, I would infinitely rather have a lobectomy with a 15 per cent chance of permanent recovery than a pneumonectomy with a 20 per cent chance of permanent recovery.

DR. WILLIAM M. TUTTLE, Detroit.—There can be no question but what it is an admirable thing to try to conserve lung tissue, but the question arises as to whether one should attempt too strongly to conserve lung tissue at the expense of leaving behind areas of carcinoma. It must be realized that we actually know very little about the lymphatic supply of the lung. A number of years ago Dr. Francis Phillips and I carried on some experiments on the lymphatic supply of the lung. These were never reported because the war interrupted the study. In pursuing this study a particulate matter was either injected into the lung parenchyma or placed endoscopically in a particular lung lobe. At varying intervals of time the nodes draining this area were chemically analyzed by a titration method. It was interesting to note in these studies that even when the testing material was deposited in a lower lobe of either lung it quickly reached the carinal nodes. If this study has virtue then it becomes evident that the lymphatic drainage of the lung is a relatively rapid process, and that under such circumstances pneumonectomy in the patient with cancer may offer a more curative procedure than lobectomy.

DR. CAHAN (closing).—I would like to thank Dr. Strieder for having raised ours from the rank of the forgotten paper.

DR. CHURCHILL (closing).—You will find that the published version of this paper carries no conclusions and no recommendations; it is a simple statement of facts and observations from which you can draw your own conclusions as obviously you have already done. The purpose is to present the raw data, without any attempt whatsoever to exclude cases or to divide them into those we thought we were going to cure and those for whom we thought we were going to make the remaining span of life more tolerable.

It is obvious that many variables determine the results in any individual effort to control cancer of the lung. Some of these variables can be identified today; others we may

not even suspect. The extent of the removal of potentially invaded lymphatic pathways and regional lymph nodes is, of course, one variable that is of prime concern to the surgeon. It is receiving new emphasis today in all cancer surgery. We must realize, however, that we are in our infancy in knowledge concerning the lymphatic structures of the lung and hilum. No precise study has been made of the normal pathways of lymphatic flow in the different segments of the lung. Mr. Allison's remark was very apt and I agree that a total pneumonectomy may be performed in a way that makes it less effective in removing lymphatic pathways than a lobectomy, combined with a mediastinal *en bloc* resection.

Other variables must include any differential mortality rate inherent in operative procedures. If a patient succumbs to operation, he achieves no benefits from having been rid of his cancer. There is also the mutilation of function touched upon by Dr. Eloesser. The time that elapses between the inception of malignancy and its excision is, of course, a potent variable.

The prowess of the individual surgeon, assuming a reasonable degree of competence, is probably the least significant of all the variables. We are all doing about the same job with about the same results.

Certain variables that we as yet are not in a position to appraise are just coming over the horizon. These center on what is called the "degree of malignancy" which is presumably an expression of interrelationships between abnormal cell and host. This is expressed as the power of autonomous growth and ability to invade and metastasize. Personally, I am quite prepared to see new knowledge completely change the relative emphasis that we as surgeons now assign to the variables on which we set such great store.

Further, in all series of cases of cancer of the lung that have been reported, we must look with great humility upon the small number of cases that we can resect today, whatever operation we employ. An outsider looking at any grouping of results could well draw the conclusion that in arguing about the extent of the operation measured in centimeters, we have lost our way among the trees that make up the forest.

I am sorry Dr. Rienhoff is not here. We have had this argument of lobectomy vs. pneumonectomy, back and forth for years. It started at Saranac Lake when I took one of his slides showing the lymphatic system of the hilum and compared it to a swamp or a morass. I have been called a scoundrel and a rascal for the last twenty years for saying that under certain circumstances I elected to perform a lobectomy for cancer. Many visitors both from this country and abroad have discussed this matter with me and their comment very often has been, "I am glad to see that you do a lobectomy occasionally, because I do too, but I don't dare say so."

A STUDY OF PULMONARY HEMODYNAMICS DURING PULMONARY RESECTION

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CARDIAC catheterization has made accessible the study of pulmonary artery and cardiac hemodynamics in human subjects with a negligible risk. Cournand, Riley, and Himmelstein[1] have studied pulmonary hemodynamics before and after pneumonectomy, in human beings, but have not observed the changes occurring during the actual operative procedure. Scarff[2] recorded pulmonary artery pressures during and after pneumonectomy in dogs. We have undertaken the study of pulmonary hemodynamics during pneumonectomy in seven cases, during lobectomy in two cases, during exploratory thoracotomy for inoperable carcinoma in one case, and during local resection of a portion of one lobe in one case. Five patients have been restudied two to six weeks after operation.

METHODS

A catheter was placed in the pulmonary artery opposite to the one to be ligated, approximately one hour before the induction of anesthesia. Basal cardiac outputs were determined by the Fick principle and initial pressures were recorded. The electrocardiogram, phase of respiration, and femoral or brachial arterial pressures were recorded simultaneously by means of a six-channel direct writing oscillograph. Subsequent observations were made at fifteen-minute intervals throughout the entire procedure, including the immediate period of ligation and after the closure of the chest. Using the Sanborn Cardioscan, the electrocardiogram was visible throughout the entire procedure.

In three cases, in which pneumonectomy was not done, the pulmonary arterial pressure measurements were obtained after temporary ligation of the pulmonary artery. In one patient a right lower lobectomy was done but the main pulmonary artery was not isolated. In the remainder of the patients, pneumonectomy was done. The pulmonary artery was first isolated and temporarily ligated, the ligature was then released. In one case the pulmonary veins were then isolated and were also temporarily ligated, and pressure readings recorded. When no appreciable change was found, this procedure was abandoned. The pulmonary artery was then ligated and divided between ligatures and the pulmonary veins were then ligated in order and divided between ligatures, and pressure readings taken following each ligation, and at the end of the procedure. Eleven days to six weeks after operation, pressures were again determined in five patients.

In one patient a catheter was temporarily introduced into the pulmonary vein that was to be ligated and thence into the left auricle (Fig. 1). No signifi-

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cant change in left atrial pressure occurred during or immediately after ligation of the pulmonary artery and veins.

RESULTS

During the induction of anesthesia, both the systolic and diastolic pressures in the pulmonary artery rose and this in some patients continued throughout the preligation period. The increase in diastolic pressure was greater than the systolic, averaging in the former 70 per cent and 36 per cent in the latter.

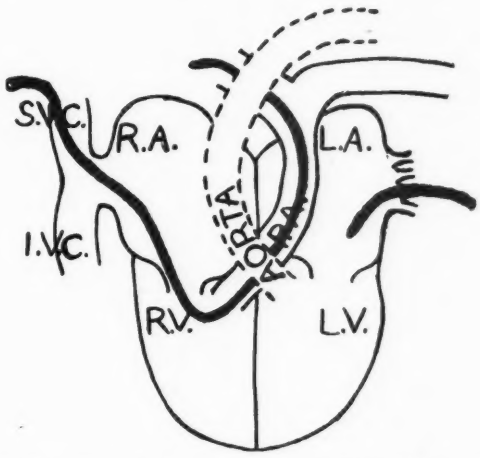


Fig. 1.—Diagram of catheters in position for taking pulmonary artery and left auricular pressures.

The rise in systolic pressure on ligation ranged from 18 to 70 per cent, the average being 40 per cent. The diastolic pressures rose from 16 to 33 per cent, except in three cases in which a decrease in diastolic pressure from 13 to 41 per cent was noted. There was a greater change in pressure, as a rule, when the right pulmonary artery was ligated as compared to the left pulmonary artery. In all except one case the pressures returned toward normal at the end of the procedure.

Table I lists the results and Fig. 2 shows the pulmonary pressures graphically in Case 8.

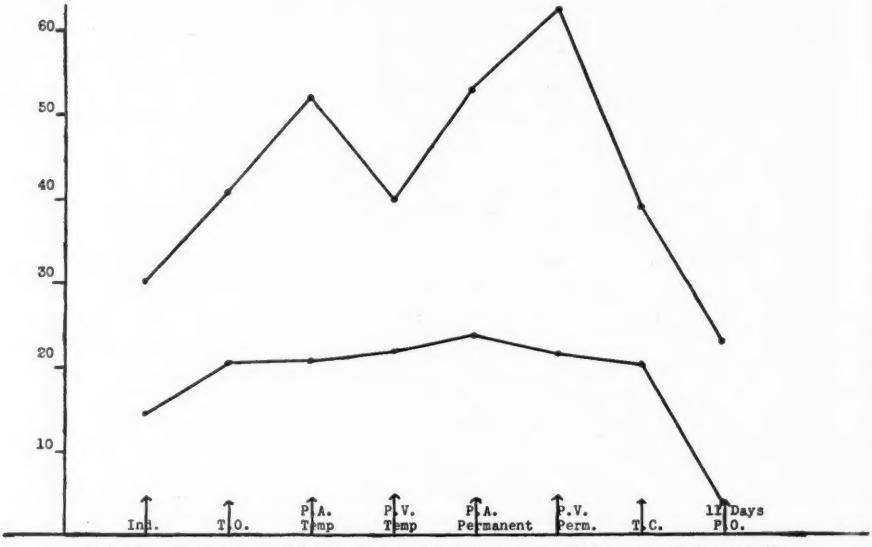
CASE NO. 5 (F. K.)—This patient deserves special comment. A 50-year-old white man had a small peripheral squamous-cell carcinoma of the left upper lobe which had manifested itself by severe hemoptysis. He was evaluated as a poor operative risk because of low cardiorespiratory reserve. This was evidenced by dyspnea on slight exertion, and a vital capacity of 42 per cent. Pulmonary artery pressure was twice normal but could be lowered by intravenous aminophyllin. Zimmerman and Scott[3] have shown that aminophyllin intravenously will significantly lower pulmonary hypertension due to a variety of causes. Because of this response to aminophyllin and because the electrocardiogram was normal and he had not been in congestive failure it was decided to operate upon him. A left upper lobectomy was done to preserve as much pulmonary function as possible. Fig. 3 shows the pulmonary artery pressures. Pressures rose with ligation of the lobar vessels and remained

TABLE I

CASE NUMBER	PATIENT		PRE-OPERATIVE	INDUCTION	THORAX OPEN	P. A. TEMPORARY	P. A. PERMANENT	CHEST CLOSED	POST-OPERATIVE
1.	M. B. 304293 54, W. M. Chr. tbc. Left pneumonectomy	P* S′		50/28	40/26 100/59	41/23 106/60	47/21	34/10	Died
2.	A. S. 303427 68, W. M. Br. Ca. Part. resection R.U.L.	P* S′	51/14 171/68	60/32 133/61	63/34 156/65	77/34 137/64		43/27 158/62	Died
3.	A. B. 306086 54, W. M. Br. Ca. Left pneumonectomy	P* S′	27/12 108/57		32/17 103/52		34/10 104/54	11/4 90/61	25/5 103/56 2 weeks
4.	W. K. 240915 54, W. M. Br. Ca. Br. Ca. Rt. pneumonectomy	P* S′			36/19 150/84	40/17 85/47	45/20	34/18	17/10 90/52 4 weeks
5.	F. K. 306727 50, M. W. Br. Ca. L.U. Lobectomy	P* S′	52/20 132/62		45/21 88/43	76/41	77/46	57/37	96/37 120/62 6 weeks
6.	H. W. 305793 49, W. F. Pulm. tbc. Left pneumonectomy	P* S′	23/8.4 157/90	41/26 164/120	40/21 170/118	35/24	39/22	31/18	25/11 158/91 12 days

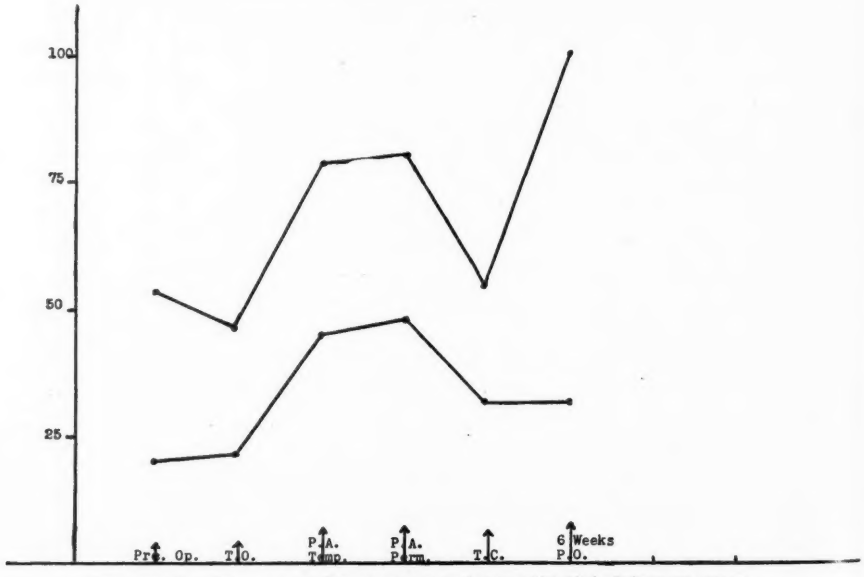
7.	J. P. 304159 30, C. M. Bronchiectasis R.L.L. and R.M. Lobectomy	P* S′	21/9	53/22	29/16 100/62		34/24 To lobe	26/17 86/50	Unable to return, working
8.	J. K. 283719 52, W. M. Br. Ca. Rt. pneumonectomy	P* S′		30/15 100/60	40/20 90/57	51/20 100/60	50/24 106/60	37/16 90/60	21/.2 135/80
9.	F. K. 300763 65, M. W. Br. Ca. Rt. Exp. Thoracotomy	P* S′		54/30 124/85	76/27			52/28	Died
10.	F. G. 309944 55, W. M. Br. Ca. Lt. pneumonectomy	P* S′	18/5 103/48	43/24	39/25	48/26 90/60	51/27 96/56	Record unsatisfactory here	Unable to recatheterize
11.	H. T. 311094 49, M. W. Br. Ca. Lt. pneumonectomy	P* S′	20/8 127/76	29/13	29/19 131/89	33/20 143/87	40/22 145/87	32/18 163/110	To be catheterized

P*—Pulmonary circulation, pulmonary artery pressure mm. Hg.
S′—Systemic circulation, systemic pressure mm. Hg.



Induction, Thorax open, Pulmonary artery tied temporarily, Pulmonary vein temporarily tied, Pulmonary artery tied permanently, Pulmonary vein tied permanently, Thorax closed, Post operatively.

Fig. 2 (Patient No. 8, J. K.).—Graph of changes in systolic and diastolic pulmonary artery pressures measured in millimeters of mercury.



Pre-operative, Thorax open, Pulmonary artery temporarily tied, Pulmonary artery permanently tied, Thorax closed, 6 Weeks post-operative.

Fig. 3 (Patient No. 5, F. K.).—Graph of changes in systolic and diastolic pulmonary artery pressures in millimeters of mercury showing marked postoperative rise.

levated. He had a stormy postoperative course with slow re-expansion of the lower lobe. He went into congestive failure and was brought out partially by digitalis, aminophyllin, and Mercuhydrin. Six weeks after the operation the pulmonary hypertension had increased. He came back to the hospital and died eight weeks after operation in congestive heart failure due to cor pulmonale.

DISCUSSION

Hickam and Cargill[4] showed that emotion and apprehension would elevate pulmonary artery pressures in unanesthetized patients. Motley and associates[5] showed that pulmonary artery pressure rose during anoxemia induced by having patients breathe 10 per cent oxygen. This may be the explanation for the rise in pressure we observed during induction of anesthesia.

Although one would expect the ligation of one pulmonary artery to throw a heavy burden on the rest of the pulmonary vascular bed and be reflected in cardiorespiratory signs elsewhere, clinically, this is rarely the case. At pneumonectomy, when the pulmonary artery is ligated, the systemic blood pressure, pulse rate, and respiratory rate and rhythm seldom change appreciably. As demonstrated in our series recorded here and by Cournand and co-workers,[1] persistent elevation of pulmonary artery pressure following resection is not common. Our only case occurred in a patient, who had an elevated pulmonary artery pressure preoperatively.

One might theorize that this patient's preoperative pulmonary artery hypertension was equivalent to a 50 per cent or more constriction of the pulmonary artery. Tigerstedt,[6] Fineberg and Wiggers,[7] Gibbon, Hopkinson, and Churchill,[8] and others have demonstrated in acute animal experiments that when the pulmonary artery is constricted more than 55 per cent, circulatory failure begins to occur. Thus in this patient further diminution of the pulmonary vascular bed by left upper lobectomy could have been a major factor in precipitating congestive cardiac failure in a patient with cor pulmonale. The determination of pulmonary artery pressures may, therefore, be of help in evaluation of poor risk patients for pulmonary resection.

SUMMARY

1. Eleven patients have been studied by intracardiac catheterization of the pulmonary artery during pneumonectomy and other intrathoracic procedures.

2. During induction of anesthesia pulmonary artery pressures rose. The average increase in the systolic pressure was 36 per cent and in the diastolic pressure was 70 per cent. The average increase in the systolic pulmonary artery pressure at the time of ligation was 40 per cent; the diastolic pressure was increased an average of 5 per cent.

3. In seven patients who had pneumonectomy, the pressure returned to normal or near normal at the end of the procedure.

4. In one patient who had a lobectomy, the pressure remained elevated and the patient died of cor pulmonale and congestive failure.

5. Catheterization of the pulmonary artery in man may prove to be an important adjunct in evaluating poor risk patients for pulmonary resection.

Acknowledgment.—We are deeply indebted for technical assistance to Gladys Heckman, R.N., and Hanna Janowskovic, R.N.

REFERENCES

1. Cournand, A., Riley, R. L., Himmelstein, A., and Austrian, R.: Pulmonary Circulation and Alveolar Ventilation Perfusion Relationships After Pneumonectomy, J. THORACIC SURG. **19:** 80, 1949.
2. Scarff, J. E.: Pulmonary Blood Pressures, Arch. Surg. **12:** 591, 1926.
3. Zimmerman, H. A., and Scott, R. W.: Personal communication.
4. Hickam, J. B., and Cargill, W. H.: Effects of Exercise on Cardiac Output and Pulmonary Arterial Pressure in Normal Persons and Patients With Cardiovascular Disease and Pulmonary Emphysema, J. Clin. Investigation **27:** 10, 1948.
5. Motley, H. L., Cournand, A., Werko, L., Himmelstein, A., and Dresdale, D.: Influence of Short Periods of Induced Acute Anoxea Upon Pulmonary Artery Pressure in Man, Am. J. Physiol. **150:** 315, 1947.
6. Tigerstedt, R.: Physiologie des Kreislaufes, Vol. 4, Berlin, 1923, W. de Gruyter & Co., p. 18.
7. Fineberg, M. H., and Wiggers, C. J.: Compensation and Failure of the Right Ventricle, Am. Heart J. **11:** 255, 1936.
8. Gibbon, J. H., Hopkinson, M., and Churchill, E. D.: Changes in the Circulation Produced by Gradual Occlusion of the Pulmonary Artery, J. Clin. Investigation **11:** 543, 1932.

DISCUSSION

DR. AARON HIMMELSTEIN, New York.—My comment on this paper is based on studies in Dr. Cournand's laboratory at Bellevue Hospital. The results reported by the essayist concerned only pulmonary arterial pressures. In any study on circulation the blood pressures reflect the relationship of flow and resistance. When Dr. McMichael was in this country last spring, he told us that Sharpey-Schaefer had demonstrated a considerable increase in cardiac output during cyclopropane anesthesia. So far we have not found this information in published form.

I would like to show one slide which bears on the problem of flow and pressures in the pulmonary circulation (slide). In this slide the circles represent data in normal subjects. The flow is calculated as one-half of the normal cardiac output; that is the flow through one pulmonary artery. The open circles represent the resting state, the flow being about 1.5 to 2 liters. On mild exercise the flow in these patients increased to 3 liters; on exhausting exercise it went up to about 4 or 4.5 liters without any rise in pressure. Therefore, the normal pulmonary vascular bed is adaptable to these changes in flow without rise in pressure. The pulmonary capillary bed is unique among all the other capillary beds in that it is exposed to atmospheric pressure and does not receive any support from surrounding structures. In the same slide the triangular figures represent patients who have had a pneumonectomy. In these patients the remaining lung was shown to be normal by studies of pulmonary function. At rest the cardiac output of 3 to 4 liters goes through one lung only. It is seen that the pressures were normal. When these patients did a moderate exercise the flow through one lung was in excess of that through each lung of the normal subjects when performing an exhausting exercise. Then the pressures began to rise. We feel that this break in the curve defines the limits of distensibility of the pulmonary vascular bed.

DR. WILLIAM E. ADAMS, Chicago.—We have been interested in this problem for some time. I think Dr. Mendelsohn has given us some excellent information in regard to the pressure in the pulmonary arteries. We have attacked this by determining the pressure within the right ventricle; of course the object is the same, to determine in patients who need pulmonary resection for neoplastic, inflammatory, or congenital lesions, as to what their "resection tolerance" might be.

(Slide.) We have been able to get our equipment together only in time to do this on five patients, and the results are shown here in four. As he has told us, the results of changes in pressure have been about as he has indicated except that they are in the right ventricle. They changed relatively little, as you see, in most cases, two figures being

given as an average. These are taken just before, during, and after ligation of the pulmonary artery. Only the first case was actually a pneumonectomy; the others happened to be inoperable carcinomas and the pulmonary artery was temporarily occluded, determining the pressures.

In the fifth case, a patient who had previously had a pneumonectomy for several arteriovenous fistulas, and had subsequently developed three or four other fistulas in the remaining lung, we removed only that portion of the lung where the fistulas were located. In this case there was a very marked rise of ventricular pressure in the right ventricle during the stage of induction of anesthesia, and somewhat less during the operation. The pressures were the same at the end of operation as at the beginning. Dr. Carlson and Dr. Charbon, my associates, have been working on this problem in animals. It is not yet ready for a complete report, but we can tell from the work so far that the pressure in the right ventricle will begin to become elevated after 50 per cent of the lung has been removed. When resection is carried further at a second operation, and it is removed to the extent of about 75 per cent, the pressures may go up as much as 100 per cent. This elevation is sustained. If it is carried further, leaving only one lobe, an upper lobe inflated, the pressures will go still higher.

A number of these animals have survived and have been followed for several months. The pressures have remained elevated. We cannot compare a normal dog's lung with the lung of a patient of advanced years where there is emphysema and degenerative changes. I would consider that a dog with 50 per cent of the normal lung removed might be in about the stage of a patient at the beginning, when we are faced with his therapy. From that standpoint, if we can determine a means of measuring his pulmonary resection tolerance by a test such as this, it will help us, especially in those cases where we have a choice of operation.

DR. JEROME HEAD, Chicago.—These studies have been very interesting in that they have helped to explain certain things which I have observed at operation. Not infrequently at the present time in resecting the lung one finds it necessary to open the pericardium and ligate the pulmonary vessels close to the chambers of the heart. In a number of the cases in which I have done this, I have noted that the heart herniates through the pericardium, often to such an extent that one fears for its integrity. This means that at this point in the operation the heart is attempting to dilate and that it is being restricted by the pericardium. It means, in other words, that often during a pneumonectomy there is a definite cardiac tamponade. The observation suggests that the pericardium has a very definite function in preventing overdilatation of the heart and that under conditions of extreme strain it confines the heart within reasonable limits and prevents cardiac damage. It suggests that one must consider the pericardium as an elastic capsule which stretches quite rapidly but quite gradually, permitting sudden strains which are thrown upon the heart to be accommodated gradually rather than suddenly.

DR. MENDELSOHN (closing).—I wish to thank Dr. Himmelstein, Dr. Adams, and Dr. Head for their comments. We are pleased that Dr. Adams' findings confirm ours. However, we do not recommend leaving a catheter tip in the right ventricle for any length of time. This is dangerous and may produce ectopic beats or rhythms.

CONSERVATIVE MANAGEMENT OF EMPYEMA FOLLOWING TOTAL PNEUMONECTOMY

EDWARD M. KENT, M.D.
PITTSBURGH, PA.

THORACIC empyema as a complication following total pneumonectomy has been a very disturbing event although one of decreasing frequency in recent years. In the majority of instances such a complication has been associated with a bronchial fistula, although about one-third of the cases to be reported herein did not have demonstrable leaks in the bronchial stump. Heretofore, it has been widespread practice to combat such an empyema by the application of established principles of surgical management. Since there is no longer a lung to be expanded, thus obliterating the infected pleural cavity, a radical thoracoplasty has been employed to achieve this end. It has been our experience that a conservative regime employing local instillation of antibiotics has made thoracoplasty unnecessary in the majority of patients treated. It is apparent that these observations are at variance with our concepts of the established rules in the surgical management of thoracic empyema; nevertheless, the results of this therapeutic regime have been very favorable in a small series of 19 patients.

There has been a certain amount of discussion concerning the role of a bronchopleural fistula as the cause of infection of the pleural space. Some believe that a postpneumonectomy infection of the pleural space which is associated with a leak in the stump of the bronchus can be considered to have occurred as a result of contamination from the tracheobronchial tree through the opening in the bronchial stump. Others believe that the bronchial fistula is the result of infection, either at the site of the closure of the bronchus or in the empty pleural space. It is my opinion that either sequence of events may take place and that, as a rule, a bronchial fistula which occurs within the first ten days after operation is a true failure of healing in the bronchial stump and that the associated empyema is of secondary origin. On the other hand, in those instances of a later leak in the bronchus, usually from three to five weeks after pneumonectomy, the cause is most commonly infection in the pleural cavity with an empyema which escapes through the recently healed bronchus. In these days of antibiotics, such an empyema is often essentially silent. Since the patient is almost always at home by this time, it has been unsuspected in most instances until the bronchus opens. Yet, the evidences of established infection are usually present at the onset of the bronchial leak, with purulent fluid present upon thoracentesis and in the expectorated material.

For purposes of analysis, the patients comprising the series to be presented herein have been divided into two groups. The first group includes those which presented an open bronchus and the second group is composed of

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those patients who developed thoracic empyema following pneumonectomy without demonstrable bronchial fistulas. The period of observation extends over the past sixty-four months.

GROUP I. EMPYEMA ASSOCIATED WITH BRONCHIAL FISTULA

Thirteen patients have been treated for thoracic empyemas accompanied by a leak of the stump of the bronchus. Success has hinged upon the fact that in every instance the bronchial fistula healed after institution of surgical treatment by means of a rib resection and open drainage. Closure of the bronchus has occurred within ten days after drainage had been established. This observation alone has been most satisfying and I cannot be certain of the causes of these observations. For repair of the bronchus at the time of pneumonectomy I have employed standardized techniques for the most part; nevertheless, a review of the method is in order.

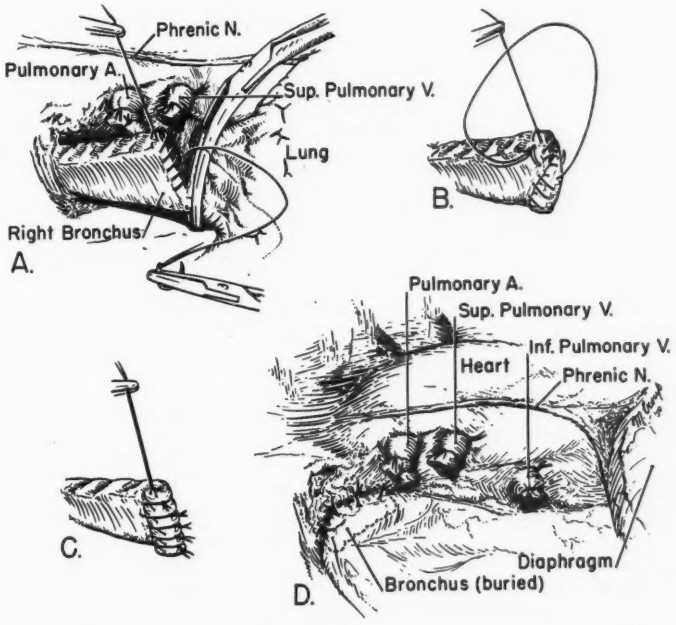

Fig. 1.—*A*, Closure of the bronchus as it is severed. No clamps are applied to proximal stump of bronchus.

B, A second row of continuous sutures is employed to fold the stump of the bronchus upon itself.

C, A row of interrupted silk sutures is placed in bronchial stump.

D, Bronchus is buried in the mediastinum.

Clamps on the proximal stump of the bronchus are avoided (Fig. 1, *A*) and a continuous suture of chromic No. 0 swaged on a curved intestinal needle is placed along the open end of the bronchial stump, step by step, as the bronchus is severed. This achieves approximation of the walls of the bronchus at the end

in precise fashion by means of shallow bites with the needle. When this row has been completed, the same suture is carried back across the end of the bronchus using deeper bites and folding the end of the bronchial stump over upon itself (Fig. 1, *B*). Last, a row of interrupted fine silk sutures is placed, and these are tied over the end of the bronchus (Fig. 1, *C*). The closed bronchial stump is then buried in the mediastinum by approximating the mediastinal pleura and whatever connective tissue is available and suitable for the purpose (Fig. 1, *D*).

It is not always possible to fold the end of the bronchus over upon itself. In some instances the stump is too short to permit folding, especially when pneumonectomy has been performed for carcinoma, and particularly when a right pneumonectomy has been done because of the short stump usually available on that side. Furthermore, the older the patient the more rigid the wall of the bronchus is likely to be and accordingly, less easily folded upon itself. I have no records to indicate which of the patients in this group had the benefits of folding over of the bronchial stump upon closure and which, if any, did not. When it was not possible to double the end of the bronchus upon itself, the closure was as described above in all other respects.

The steps in the plan of treatment consist of the following:

1. Thoracostomy for surgical drainage.
2. Instillation of antibiotics through the drainage tube after the bronchial fistula has closed.
3. Removal of the tube and continued instillation of antibiotics into the pleural cavity through the chest wall.

In the presence of a bronchial fistula, cultures of the empyema fluid customarily reveal mixed infections to be present. Once the opening in the bronchus has closed, antibiotics are instilled into the pleural cavity through the drainage tube. An empirical dosage including 200,000 units of penicillin and one-half gram of streptomycin has been employed in a single daily administration. This is continued until the drainage has become reduced in volume and less purulent in character. Cultures are taken periodically and when the preceding changes in amount and character of the drainage can be coupled with bacteriologic cultures yielding a change of flora, the drainage tube is removed. Thereafter, the same dosage of antibiotics is instilled into the pleural space through the chest wall, usually in the second interspace anteriorly. The change in flora noted previously commonly shows one of the staphylococci or other organisms which may be considered as contaminants. The time period for this step has averaged ten days.

In some instances, loculations and fibrin masses will be present in the pleural cavity when the bronchus has healed. Under these circumstances, Dakin's solution has been employed as an irrigant twice daily until the empyema space has been cleansed of all such media for bacterial growth. Fluoroscopic examination and thoracoscopic inspection through the drainage tract will yield the necessary information in this regard. Antibiotic therapy is delayed until this has been accomplished in those instances in which loculation and fibrin deposits have persisted.

Once the tube has been removed, the use of antibiotics by injection into the pleural cavity is continued as a single daily dose for one week. The patient is then observed a few additional days for any evidence of fever and by fluoroscopic examination for indications of an increase in the amount of fluid in the pleural cavity. In no case has either finding been observed.

In this group of 13 patients, the fistula occurred within ten days in 6, and after a longer period in 7 (Table I). As has been stated previously, the fistula closed in each instance after surgical drainage had been established. One patient experienced a recurrence of the empyema three and one-half months after release from the hospital but without reopening of the bronchus. He was treated successfully a second time by the same method and has remained well for twenty-two months. A second patient had a recurrence of empyema without fistula and has refused to undergo a second course of treatment or a thoracoplasty. He is still wearing a drainage tube. A third patient was treated as an ambulatory out-patient, at my suggestion, by his personal physician. A recurrence was experienced shortly after the tube was removed, which was successfully treated at a later date. The details of this case are to be presented more completely because of the unusual observation that the empyema first occurred nineteen months after pneumonectomy. A fourth patient was treated by this method but the character, volume, and cultural findings were not influenced by therapy and a thoracoplasty was performed. At the time, neither bacitracin nor aureomycin was available and in the light of recent experiences, I believe he might have been treated successfully by these newer antibiotics. This case will be presented in some detail also because the empyema occurred eight months after pneumonectomy had been performed.

Therefore, in this group of 13 patients, 11 were cured of empyema by conservative means while 1 required a thoracoplasty and 1 is still carrying a thoracostomy tube after a recurrence of empyema following therapy. Two

TABLE I. RESULTS OF TREATMENT IN THIRTEEN PATIENTS WHO DEVELOPED BRONCHIAL FISTULAS AND EMPYEMAS AFTER TOTAL PNEUMONECTOMY (A MIXED INFECTION WAS PRESENT IN ALL CASES)

PATIENT	AGE (YEARS)	PATHOLOGY	ONSET OF EMPYEMA AFTER PNEUMONECTOMY	RESULT	COMMENT
1. W. C.	28	Lung abscess	8 months	Failure	Thoracoplasty
2. O. R.	50	Carcinoma	19 months	Cure	1 recurrence, cured
3. W. B.	64	Carcinoma	5 weeks	Recurrence	Refuses further treatment
4. A. J.	60	Carcinoma	10 days	Cure	Successful treatment after one recurrence
5. B. L.	52	Carcinoma	8 days	Cure	
6. F. R.	46	Carcinoma	7 days	Cure	
7. E. D.	49	Carcinoma	10 days	Cure	
8. J. R.	36	Bronchiectasis	9 days	Cure	
9. L. S.	56	Carcinoma	8 days	Cure	
10. J. B.	48	Multiple abscesses	4 weeks	Cure	
11. R. D.	46	Carcinoma	5½ weeks	Cure	
12. J. K.	26	Bronchiectasis	4½ weeks	Cure	
13. B. F.	39	Lung abscess	6½ weeks	Cure	

additional patients in this group experienced recurrence of the empyema but both were cured by a second course of therapy.

Bacteriologic control of progress of treatment can be provided with ease in most instances during the last phase of therapy. When the needle is inserted into the pleural cavity for the purpose of injecting the antibiotics, a specimen of the pleural fluid may be obtained first and culture studies can be made. This also permits observation of changes in the gross character of the residual effusion. Usually, the fluid soon becomes thin and clear but retains the color of the antibiotics. However, in three patients, aureomycin has been introduced into the cavity and the fluid has become grossly bloody in each instance.

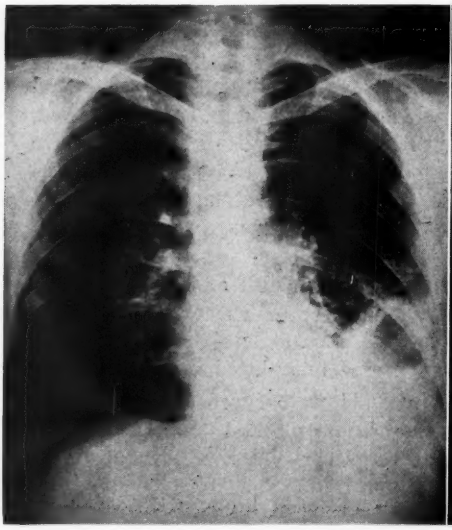

Fig. 2.

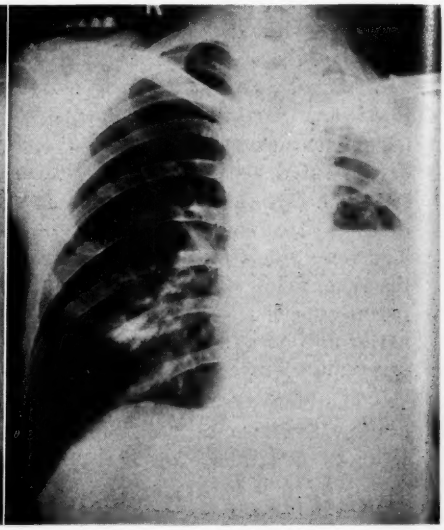

Fig. 3.

Fig. 2.—Roentgenogram of chest showing large, thick-walled cavity in lower left lung.
Fig. 3.—Roentgenogram of chest showing fluid level in left thoracic cavity and infection of remaining right lung.

CASE REPORTS

Case No. 1.—W. C., male, aged 28 years, was admitted to the hospital with symptoms of pulmonary suppuration which had persisted for three months. The cause of onset was unknown. Marked pulmonary osteoarthropathy was manifest in many joints. A chest film revealed a large, thick-walled cavity, apparently limited to the left lower lobe. After thorough study, a diagnosis of pulmonary abscess was made and an aggressive course of therapy was pursued. Despite adequate treatment, the abscess cavity persisted (Fig. 2) and the symptoms continued with little change. Accordingly, resection of the left lower lobe was decided upon and operation was performed April 7, 1948. At the time of operation, it was established that the abscess cavity had extended across the interlobar fissure into the lingula of the upper lobe and that a large excavation had occurred in this segment. A total pneumonectomy was performed and an uneventful convalescence was marked by very rapid disappearance of the signs and symptoms of pulmonary osteoarthropathy. Eight

months later, the patient was readmitted to the hospital. He then presented a history of very marked recurrence of the symptoms of pulmonary suppuration with the onset having taken place ten days previously. Clinical evaluation soon demonstrated the presence of empyema (mixed infection) in the left pleural space, an associated fistula in the bronchial stump, and spill-over infection of the right lung (Fig. 3). Drainage of the left empyema was performed at once and bronchoscopic aspiration for the infection in the right lung soon followed. Systemic antibiotic therapy had been instituted upon admission to the hospital. The infection in the right lung cleared rapidly and the fistula in the bronchial stump closed within seven days. Attempts were made to employ the conservative regime of antibiotic therapy by instillation into the pleural cavity, using both penicillin and streptomycin. The volume, character, and culture characteristics were not affected by treatment and a thoracoplasty was performed. If aureomycin or bacitracin, or both, had been available for use, it might well have been possible to avoid thoracoplasty.

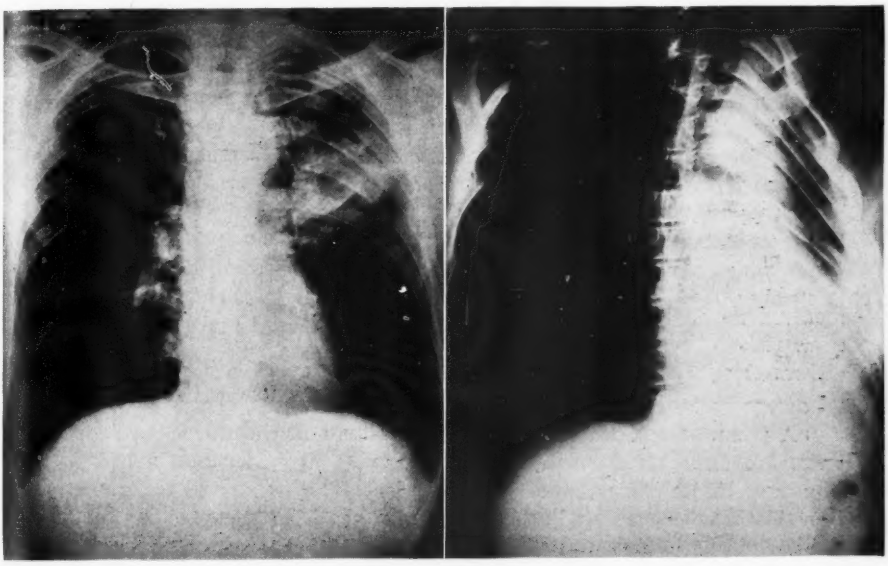

Fig. 4. Fig. 5.

Fig. 4.—Roentgenogram of chest showing mass in left upper lobe. This was proved to be due to squamous-cell carcinoma.

Fig. 5.—Roentgenogram of chest showing empty left thoracic cavity after evacuation of of contents through the stump of the bronchus twenty-two months following total pneumonectomy.

CASE NO. 2.—O. R., male, aged 50 years, was admitted to the hospital on April 4, 1947 with a history of cough, expectoration, and hemoptysis of three months' duration. Clinical study established a diagnosis of squamous-cell carcinoma, left upper lobe bronchus (Fig. 4). A left total pneumonectomy was performed on April 11, 1947, and an uneventful convalescence followed. Nineteen months later, there was sudden onset of fever of unexplained origin which was treated by penicillin, aureomycin, and streptomycin in large doses. The fever persisted until early February, 1949, at which time the patient coughed up a large quantity of bloody pus. Thereafter, cough persisted but the temperature was normal. He was readmitted to the hospital on March 3, 1949, and clinical study revealed an empyema on the left side (Fig. 5) with a fistula in the bronchial stump. Rib resection was performed and open drainage was established. The bronchial fistula healed promptly

and the patient was released from the hospital after arrangements had been made for treatment of the empyema cavity by instillation of penicillin and streptomycin under the guidance of his own physician in his home city. However, when the tube was removed, a recurrence of fever was noticed within twenty-four hours and the tube was reinserted by his physician within seventy-two hours. The patient elected to carry the drainage tube for eleven months, after which he returned to the hospital under my care for a thoracoplasty. After discussing the problem, the patient elected to accept one more attempt to correct the left empyema by conservative means. Since both penicillin and streptomycin had been introduced into the thoracostomy tube daily during the entire period, it was assumed that the invading organisms had developed resistance to these antibiotics. Consequently, it was decided to employ bacitracin in doses of 25,000 units daily as long as the drainage tube was in place. After the tube was removed, this drug was replaced by aureomycin (soluble, for parenteral use) in doses of 100 mg. daily into the pleural cavity. A good result was achieved on this attempt and the patient has been well for four and one-half months. Since the first empyema was so late, it may be said that it is still too early to be certain of the end result.

In addition to this group of 13 patients who have developed empyemas and bronchial fistulas after total pneumonectomy, three more instances of leakage of the bronchial stump have been experienced but none has been treated by this method for differing reasons. One patient died of suffocation on the day the bronchus failed (fifteen days after pneumonectomy for carcinoma). A second patient never developed infection of the pleural space, and a plastic closure of the bronchial fistula was performed. The third patient still has a bronchial fistula which occurred one month after right pneumonectomy for carcinoma in September, 1949; there is evidence of advancing metastases and I suspect that a recurrence in the stump may have caused the fistula and probably explains the failure of the bronchus to heal.

GROUP II. EMPYEMA WITHOUT BRONCHIAL FISTULA

A group of 6 patients have been observed, all of whom have developed empyema following total pneumonectomy but without evidence of a leak in the bronchus. With the exception of one patient, all were proved to have a pure infection after culture studies (Table II). In each instance, the empyema was not manifested for at least a month after operation. The same program of treat-

TABLE II. RESULTS OF TREATMENT IN SIX PATIENTS WHO DEVELOPED EMPYEMAS WITHOUT BRONCHIAL FISTULAS AFTER TOTAL PNEUMONECTOMY (PURE INFECTION IN FIVE CASES, MIXED INFECTION IN ONE CASE)

	PATIENT	AGE (YEARS)	PATHOLOGY	ONSET OF EMPYEMA AFTER PNEUMONECTOMY (DAYS)	RESULT	COMMENT
14.	A. C.	44	Carcinoma	105	Failure	2 recurrences (hemolytic *Staph. aureus*)
15.	W. H.	61	Carcinoma	35	Cure	Empyema necessitatis. (mixed infection)
16.	M. Y.	46	Bronchiectasis	16	Cure	(Hemolytic *Staph. aureus*)
17.	B. K.	60	Carcinoma	38	Cure	(Pneumococcus) Empyema necessitans
18.	R. L.	29	Lung abscess	26	Cure	(Hemolytic *Staph. auerus*)
19.	F. R.	48	Carcinoma	19	Cure	(*Stap. albus*)

ment has been pursued except that it has been unnecessary to await closure of a bronchial fistula after drainage of the empyema. All have responded well to therapy, except one patient who has had two recurrences as reported below.

CASE REPORT

CASE No. 14.—A. C., female, aged 44 years, was admitted to the hospital June 8, 1947, with a history of cough, expectoration, hemoptysis, fever, and weight loss. Bronchoscopy and biopsy yielded a diagnosis of carcinoma of the right main bronchus. A right total pneumonectomy was performed which was followed by an uneventful convalescence. Sixteen weeks later she was readmitted to the hospital with a history of onset of high temperature five days previously. A diagnosis of right empyema was established and drainage by rib resection was employed. A program of local instillation of antibiotics (penicillin and streptomycin) was pursued with a good initial result. The cultures had shown pure growth of a hemolytic *Staphylococcus aureus*. Three months after her return home, a similar episode occurred and spontaneous evacuation of pus took place through the site of the rib resection which had been performed previously. She was readmitted to the hospital and a second regime of local antibiotic therapy was carried out. The cultures at the time of recurrence again revealed pure growth of a hemolytic *Staph. aureus*. A good primary result was achieved once more and the patient was released from the hospital only to experience a second recurrence three months later. Once more the cultures revealed only a hemolytic *Staph. aureus*. After drainage had been re-established, a thoracoplasty was performed with subsequent control of the empyema.

DISCUSSION

The treatment of empyema thoracis by the use of antibiotics and without surgical drainage has met varying responses. Blades, Hamilton, and Dugan,[1] Roberts, Tubbs, and Bates,[2] and Poppe[3] have reported unfavorably on the matter while Burnett, Rosemond, Hall, and Caswell,[4] Lockwood, White, and Murphy,[5] and Hirshfeld, Boggs, Abbott, and Pilling[6] have recorded promising results. It has been my experience that such a plan of conservative management is effective if the empyema is not too extensive, if treatment is begun early in the course of the disease, if there is no loculation, if the pus is not thick, and if adequate, aggressive therapy is applied throughout the treatment period. In brief, the factors must be such that prompt and complete re-expansion of the lung is achieved while aspiration therapy is employed. If obliteration of the pleural space cannot be effected readily, treatment is likely to fail or the end results may be unsatisfactory.

After total pneumonectomy has been performed, there is no lung to obliterate the pleural cavity in combating infection of that space. Therefore, the essential mechanism of healing in empyema thoracis cannot be brought about, and in order that the space may be obliterated, a thoracoplasty has been deemed mandatory. The studies reported indicate that it is not always necessary to obliterate the pleural space in order to cure an empyema which follows total pneumonectomy, provided there is no leak in the bronchial stump. I cannot conceive of this form of treatment being either safe or successful if a bronchial fistula is present.

The bacteriologic procedures which have been employed in this study have been limited in scope and application. For example, no tests have been carried out to ascertain the degree of sensitivity of organisms to antibiotics.

Certainly more adequate use of the techniques practiced in bacteriology will extend the effectiveness of such therapeutic measures as these.

SUMMARY

1. The conservative treatment of empyema following total pneumonectomy has been outlined.

2. Nineteen patients have been treated by this method with sixteen successful end results. There has been no mortality.

3. Three patients have been followed for five months or less, the remaining thirteen patients have been observed for nine or more months.

4. Bronchial fistulas associated with empyemas have been found to heal after surgical drainage of the infected pleural space.

5. More adequate use of the techniques of bacteriology should improve the results of this form of treatment.

REFERENCES

1. Blades, Brian, Hamilton, J. E., and Dugan, D. J.: Observations On Treatment of Empyema Thoracis With Penicillin, Surgery **17**: 572, 1945.
2. Roberts, J. E. N., Tubbs, O. S., and Bates, M.: Pleural and Pulmonary Suppuration Treated With Penicillin, Lancet **1**: 39, 1945.
3. Poppe, J. K.: Limitations of Penicillin in Treating Empyema, J. A. M. A. **129**: 435, 1945.
4. Burnett, W. E., Rosemond, G. P., Hall, J. H., and Caswell, H. T.: Treatment of Empyema With Topical and Systemic Penicillin and Other Antibacterial Agents, Surg., Gynec. & Obst. **87**: 44, 1948.
5. Lockwood, J. S., White, W. L., and Murphy, F. D.: Use of Penicillin in Surgical Infections, Ann. Surg. **120**: 311, 1944.
6. Hirshfeld, J. W., Boggs, C. W., Abbott, W. E., and Pilling, M. A.: Value of Penicillin in Treatment of Empyema, J. A. M. A. **128**: 577, 1945.

DISCUSSION

DR. DAVID WATERMAN, Knoxville, Tenn.—I am impressed in two ways by this excellent paper of Dr. Kent's. In the first place I think it illustrates again the fact that our concepts of clinical therapy are still in a fluid state with regard to antibiotic therapy. In the second place, I think it demonstrates one of the primary obligations of the surgeon—to avoid surgery if that is possible. Generally speaking, the principle of drainage, of course, is still a valid one. Occasionally, in an early empyema occurring after pneumonectomy, even open drainage may be circumvented, despite the fact that it has been unequivocally stated that obliteration of the pleural space is essential if the empyema is to be healed. I would like to show slides of a case illustrative of such an instance, done a number of years before we realized the usual limitations of antibiotic therapy.

(Slide.) This is a 43-year-old man who came to us six years ago with multiple lung abscesses involving all three lobes on the right. He was desperately ill, and had to go through a long period of hospitalization with repeated bronchoscopies before he could be safely brought to surgery. (Slide.) This is the injection of the pneumonectomy specimen showing almost complete destruction of the normal architecture of the lung. As I recall there were 16 cavities present. (Slide.) A few days postoperatively, at the time the roentgenogram shown here was taken, he developed staphylococcus empyema.

Being brash in those days because of the early reports on the use of penicillin in empyema, we attempted to treat the patient conservatively without drainage, and injected penicillin daily into the pleural space in the same way we may very occasionally successfully do it in early postpneumonia empyema.

After some ten days of treatment, several sterile cultures were returned, and the patient was sent home. About two weeks later he had a recurrence of empyema and came back into the hospital. Again he was treated conservatively, and the empyema was success

fully sterilized in spite of the fact that a large free pleural space continued for some time thereafter. (Slide.) Here is the final result more than five years after therapy. The patient has been well and working during this entire period.

The essential requirement for such results, of course, is an early empyema caused by a penicillin-sensitive organism. Once loculation has occurred, drainage is obligatory.

As to the bronchial closure Dr. Kent has described, I do not think the type of suture is as important as the avoidance of bronchial traumatization, and the adequate covering of the stump. For several years we have used with marked success a free pleural graft tied over the cut edge of the bronchus with the bronchial closure sutures. This interposes an effective barrier between the bronchus and the surrounding vascular structures. Should a stump abscess occur, the danger of erosion into a vessel is lessened, we believe.

DR. L. R. DAVIDSON, New York.—In that Dr. Kent has presented the problem of bronchopleural fistula and its complications, it gives me an opportunity to tell of a conservative method of therapy which has been used at Seaview Hospital at the instance of Dr. Warner. Taken from the pathologic sense we have applied it clinically. It is well known that lye or sodium hydroxide is markedly sclerotic. Therefore, with that in mind, Dr. Warner suggested the application of a bead of sodium hydroxide to the bronchial stump. In these cases of bronchopleural fistulas following excisional surgery, the results to date, so far as I could gather shortly before I left New York, were as follows:

The total number of cases treated, 24; closures to date, 15; patients in good condition, sputum negative and fistula closing, 2; closing, but contralateral lesion with positive sputum, 3; patient in good condition, bronchus closing clinically, 1; 4 deaths.

If you add those figures, although I mentioned 24 cases, the figure will be 25, the reason for the discrepancy being that one case after closure died of a spontaneous pneumothorax on the opposite side. We have had some cases where, in the presence of a contralateral pneumothorax, we have gone ahead and performed pneumonectomy.

The method of treatment is this: One takes a metal stylet, heats it, puts it into a can of lye and forms a bead. Through the bronchoscope the bead is applied to the stump, and after 30 to 45 seconds a sponge upon a bronchoscopic holder, saturated and then dried, with 6 per cent acetic acid, is applied to the area originally touched by the sodium hydroxide; that is to neutralize it. Applications are made usually two to three weeks apart and, on the average, two to three applications are necessary.

We mention this procedure with no particular claim for oringinality or for success, but merely as a method of attempting to close these bronchopleural fistulas, which do occur regardless of the technique of closure for pulmonary tuberculosis.

DR. JOSEPH WEINBERG, Van Nuys, Calif.—Dr. Kent has reported excellent results in the treatment of chronic empyema by a carefully planned method of antibiotic therapy. However, it should be kept in mind that the period of follow-up observation is short, and it is too early to predict that the empyemas so treated will remain healed. It has been a not uncommon experience to have empyemas supposedly healed by antibiotic therapy, particularly penicillin therapy, recur after a dormant period of months or years. Especially has this been the case in those patients in whom the pleural space has not been obliterated. Whether this will be the case with Dr. Kent's more studied plan of treatment with antibiotics other than penicillin remains to be seen.

A most welcome phase of the treatment described is the closure of bronchial fistula which may coexist with the empyema. For those cases in which the bronchial fistula fails to close with nonsurgical treatment, I wish to present a simple surgical method of effecting closure. The thickened parietal pleura which surrounds the fistulous opening is removed by decortication— preferably removing the entire parietal pleural membrane to favor healing of the coexisting empyema. This leaves a cuff of the bronchus projecting into the pleural space. One can then close the bronchus by suture according to his preferred method. We have successfully closed two fistulas in this manner. One followed pneumonectomy for carcinoma, with repair ten months after pneumonectomy. The other followed pneumonectomy for abscess associated with extensive bronchiectasis, with repair approximately two years after resection. The fistulas remain closed ten months and one month, respectively, after repair.

THE UTILIZATION OF STREPTOKINASE-STREPTODORNASE

In a Patient With Hemopneumothorax and a Patient With Postpneumonectomy Sanguineous Coagulum

C. Thomas Read, M.D. (by invitation), and F. B. Berry, M.D.
New York, N. Y.

THE rapid lysis of blood clots and related coagulum of exudates takes place, as shown by Tillett and Sherry,[1] when concentrated and partially purified preparations derived from broth cultures of hemolytic streptococci are instilled into them. These preparations are unique in their action in that they show rapid lysis of fibrin clots, alter fibrinogen so that it no longer forms fibrin, and cause the insoluble fibrouslike nucleoprotein found in purulent collections to dissolve.

The fibrinolytic activity of hemolytic streptococci was discovered by Tillett and Garner[2] but only recently has this property been extensively purified and concentrated by Christensen.[3] The filtrates containing the active principles are recovered from broth cultures in large amounts, free of bacteria. More recently Sherry, Tillett, and Christensen[4] showed a significant constituent present in pus consisted of desoxyribonucleoprotein, forming 30 to 70 per cent of purulent sediment. Tillett, Sherry, and Christensen[5] demonstrated a second enzyme, streptodornase, that changed the thick viscid nucleoprotein to a thin solution.

The streptococcal fibrinolysin product has been termed "Streptokinase" and the nucleoprotein lysing factor "Streptodornase."

Although the enzymatic activity is chiefly present in human Group A hemolytic streptococci, the products under discussion are derived from the Lancefield Group C, H46A strain since it is a nonpathogen for man and would, therefore, be least likely to obscure the clinical picture by any serious toxic side-reactions.

Streptokinase acts very much like a catalyst but it is depleted as the dissolution of the parent substance takes place. Consequently its action in patients is self-terminating. It has been shown that a precursor present in bloody collections and exudates termed plasminogen or activatable fibrin-lysing system is needed to effect fibrin lysis. This is illustrated in experimental studies by the failure of a clot to lyse when highly purified fibrinogen and thrombin are mixed with SK (streptokinase). However, with the addition of plasma Fraction III, which contains the plasminogen, lysis occurs quickly. No activatable substance is required for the lysis of the nucleoprotein per se since SD (streptodornase) is an active enzyme.

From the Chest Surgical Service, Columbia University College of Physicians & Surgeons, Bellevue Hospital, and the Third Medical and Surgical Divisions, New York University College of Medicine, Bellevue Hospital.

This study was supported under a contract with the Department of the Army, Office of the Surgeon General United States Army.

Read before the Thirtieth Annual Meeting of The American Association for Thoracic Surgery, Denver, Colo., April 15-18, 1950.

The enzymes used in the early studies were produced in the laboratory of Dr. Christensen but more recently sufficient amounts are being manufactured commercially* to carry on large scale clinical studies. The details of the purification and the original investigative results with the enzymes appear in earlier reports by Tillett and Sherry[1, 5, 6, 7] and Christensen.[8] In a forthcoming report by Tillett, Sherry, and their associates† a comprehensive analysis of the dosage, laboratory findings, and a review of clinical data relative to hemothorax will be discussed.

The enzymes as now prepared in lyophilized form appear mixed together with varying amounts of either increment but usually with predominant portions of SK. Although probably not required in cases of hemothorax the presence of SD is not contraindicated nor does it detract from the action of SK. In this report we are essentially interested in the clinical application of SK.

On the Chest Surgical Service, and others, at Bellevue Hospital and at neighboring institutions where the material has been allotted by and used under the direction of Dr. W. S. Tillett and those associated in the work, SK has been used in a number of patients. The results for the most part have been good and in several instances dramatic. Two cases of this group are described here in which it was used.

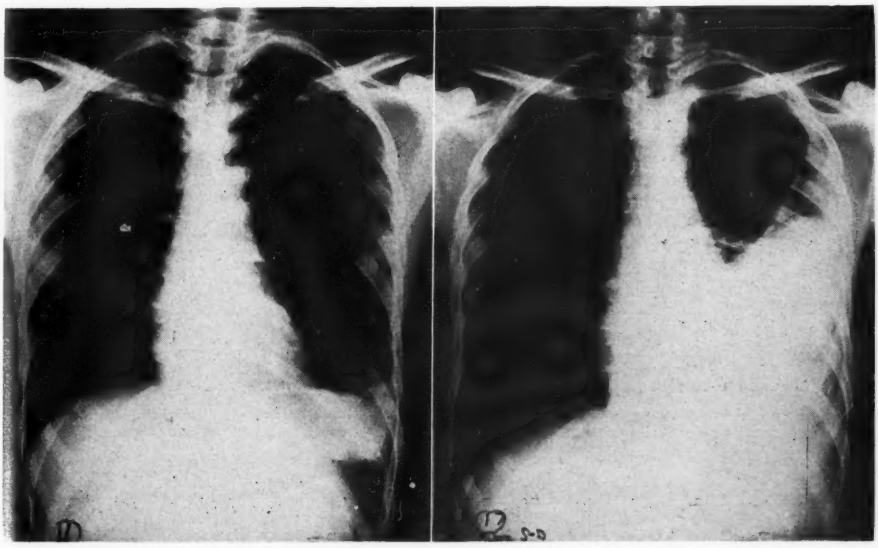

Fig. 1. Fig. 2.

Fig. 1 (Patient M.L.).—X-ray appearance on the day of admission showing about 40 per cent pneumothorax and a small amount of fluid at the left costophrenic angle. Subsequent to this film a large accumulation of blood appeared in the space.

Fig. 2 (Patient M.L.).—Roentgenogram of chest taken on the seventeenth hospital day just before the use of enzyme therapy, showing an extensive density from which only small quantities of bloody fluid could be aspirated on numerous attempts.

*Lederle Laboratories, Inc., Pearl River, N. Y.

†In preparation, Tillett and co-workers.

CASE REPORTS

PATIENT M. L.—This 21-year-old colored man,* without any previous pulmonary complaints, was admitted on Sept. 8, 1949, to St. Vincent's Hospital two hours after the acute onset of pain in the left chest. There were no other symptoms. The admission x-ray and fluoroscopic examination showed a 40 per cent pneumothorax in the left hemithorax and a small collection of fluid at the costophrenic angle (Fig. 1).

On Sept. 9, 1949, the roentgenogram showed about an 80 per cent hydropneumothorax; 1,200 c.c. of bloody fluid and air were aspirated from the hemothorax and a similar yield was obtained the following day. At this time his temperature ranged between 101° to 102° F. but all cultures of fluid withdrawn were negative.

Thereafter only small quantities of serosanguineous fluid could be aspirated. By the seventeenth hospital day, the roentgenogram still revealed an extensive coagulum in the left chest (Fig. 2).

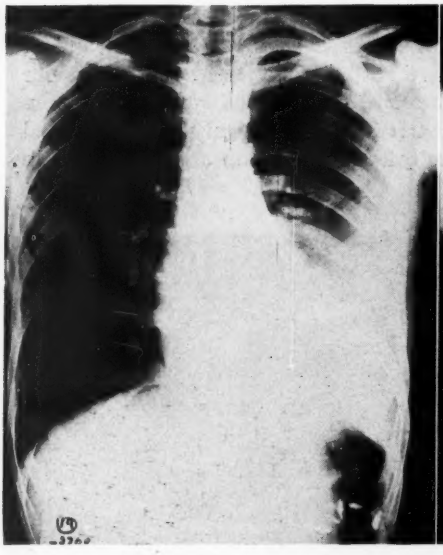

Fig. 3.

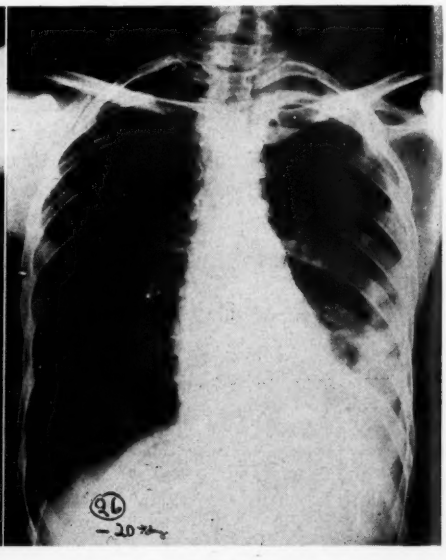

Fig. 4.

Fig. 3 (Patient M.L.).—Roentgenogram of chest taken two days after Streptokinase injection, and following the aspiration of 2,700 c.c. of bloody fluid. There is a noticeable decrease in the size of the density.

Fig. 4 (Patient M.L.).—Posteroanterior roentgenogram of chest on the twentieth hospital day following further aspirations and one day before the second instillation of SK-SD. A striking clearing in the left hemithorax is shown.

At this time ampules of enzyme concentrate, each containing 250,000 units SK and 3,000 units SD were instilled simultaneously in three separate sites. During the next two days 2,700 c.c. of bloody fluid were aspirated (Fig. 3).

The injection was repeated on the twenty-first hospital day with a subsequent yield of 1,145 c.c. over the next three days (Fig. 4).

On Oct. 15, 1949, the thirty-eighth hospital day, a marked improvement had occurred in the physical findings and the x-ray appearance, and the patient was discharged (Fig. 5).

He was studied for pulmonary function Nov. 7, 1949, shortly after discharge from the hospital, which revealed a moderate reduction in ventilation and oxygen uptake on the affected side, especially on exercise.

*St. Vincent's Hospital, courtesy of Dr. Francis W. Baldwin.

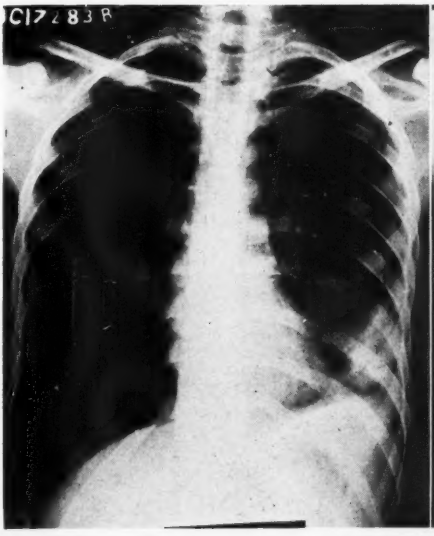

Fig. 5.

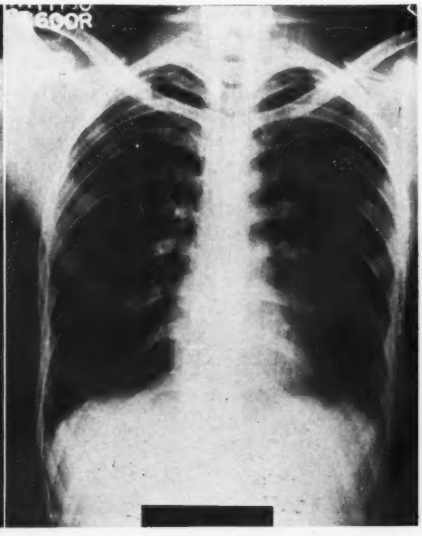

Fig. 6.

Fig. 5 (Patient M.L.).—The appearance of the x-ray photograph at the time the patient was discharged from the hospital. It is to be noted a small residual density remains in the left costophrenic angle. Shortly after this view was taken he had a pulmonary function study at which time a similar roentgenogram was seen.

Fig. 6 (Patient M.L.).—Roentgenogram of chest at follow-up approximately three months following admission to the hospital. There is now complete clearing. Inspiration and expiration films showed definite changes in the level of the diaphragm indicating motion of the diaphragm.

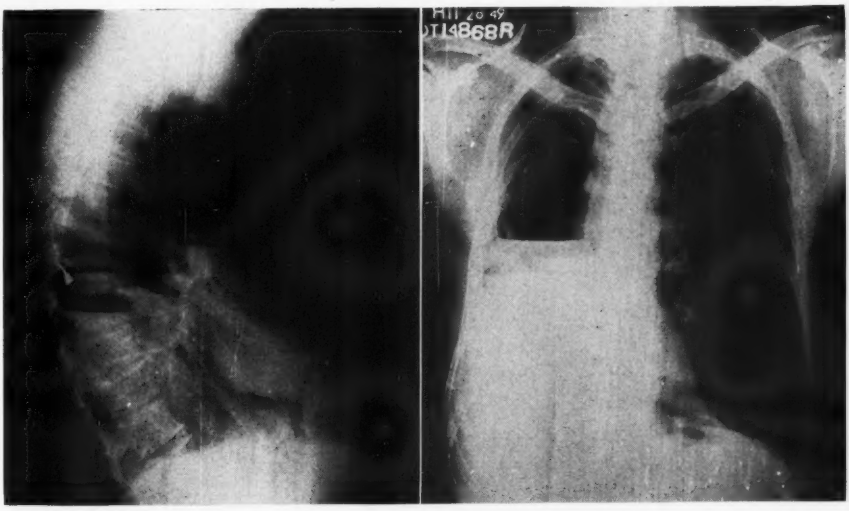

Fig. 7 (Patient D.McG.).—Posteroanterior and right lateral roentgenograms on the forty-fifth postoperative day just before the injection of streptokinase, revealing the loculated hemothorax from which only a few cubic centimeters of bloody fluid could be aspirated.

Subsequent to this study the patient showed marked clearing by x-ray and fluoroscopy examination, with good diaphragm motion and clinical evidence of normal ventilation (Fig. 6). Unfortunately he would not submit to a final bronchospirometric study.

PATIENT D. MCG.—This 62-year-old white man was admitted to Bellevue Hospital with symptoms and x-ray evidence of a neoplasm in the right upper lobe region. Bronchoscopic biopsy disclosed a carcinoma in the right upper left bronchus. On Nov. 4, 1949, a right pneumonectomy was performed with an uneventful postoperative course until the thirty-

Fig. 8 (Patient D.McG.).—The x-ray appearance following removal of 1,450 c.c. of bloody fluid. There is an area of density remaining in the lower right hemithorax that communicates with the main cavity but there is practically no fluid present.

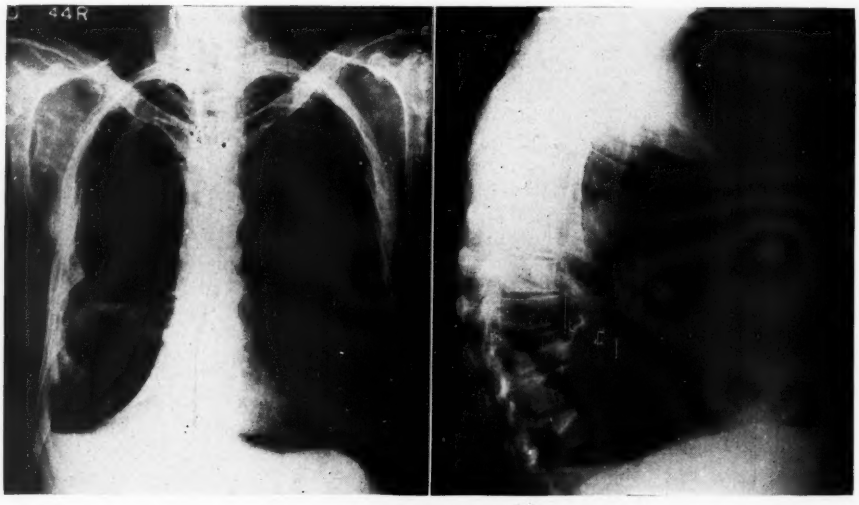

Fig. 9 (Patient D.McG.).—Roentgenograms taken at the end of enzyme therapy following the eradication of the infected hemothorax. It is to be noted that there is further resolution of the density in the lower right chest.

nineth day when his temperature began to range from 101 to 102° F. At this time the roentgenogram showed multiple fluid levels in the right hemothorax and only small quantities of bloody fluid could be aspirated (Fig. 7). The cultures of this fluid were negative for pyogens.

On the forty-fifth postoperative day, because an infected hemothorax was suspected, ampules of SK, 150,000 units, and SD, 60,000 units, were injected into two sites. Twenty-four hours later 800 c.c. of bloody fluid were removed from the right chest and the next day 650 c.c. were obtained (Fig. 8). Each of these specimens cultured out *Escherichia coli.*

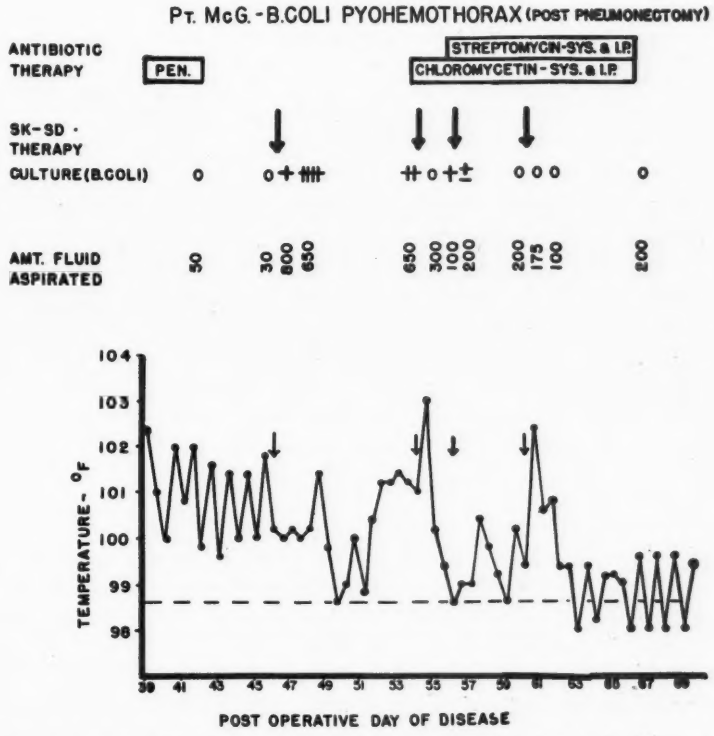

Fig. 10 (Patient D.McG.).—Temperature course, quantitative bacterial cultures, amounts of chest fluid aspirated, periods of antibiotic therapy and the days SK-SD was given (arrows) are illustrated. Note the appearance of *Escherichia coli* after first SK-SD instillation and subsequently its rapid sterilization with combined enzymatic antibiotic therapy.

During the next two days the patient's temperature returned to normal but unfortunately with the intervening holidays the treatment was not pursued and he again became febrile with temperature reaching 103° F. On Dec. 28, 1949 (fifty-third postoperative day), four days following the last aspiration, thoracentesis yielded sanguinopurulent fluid which was still positive for *E. coli* on culture. An injection of enzyme was made then and repeated on alternate days on two subsequent occasions. On the intervening days Chloromycetin and streptomycin were instilled into the chest and at the same time administered systemically. After the third injection of enzyme the cultures were negative and following the fourth instillation of SK-SD his temperature returned to normal and remained there (Fig. 9). Fig. 10 describes the clinical and bacteriological findings in this case. He subsequently underwent two stages of thoracoplasty and has remained free from further evidence of the injection.

DISCUSSION

Whenever blood appears in the thorax there is a good possibility that it will clot despite early attempts at aspiration, and frequently it is permitted to remain unmolested with the hope that it will resolve spontaneously. Large accumulations often defy prompt attempts at complete aspirations as they assume a gel form, and therefore demand more attention than small collections which frequently vanish without any treatment. Massive clotting has been observed four to six hours following trauma[9] and in less time when secondary thoracotomy has been mandatory subsequent to an initial procedure.[10] In such instances aspiration will be of little avail.

Fibroblastic proliferation within a clot, which may appear within five days,[11] leads to organization and this in turn precludes further conservative management. Such evidence should prompt one to evacuate the hemothorax as soon as possible.

Little has been added to the management of hemothorax since the excellent observations of Tuttle, Langston, and Crowley[12] and Samson, Burford, Brewer, and Burbank[13] and others reporting during the war years. These authors suggested that about 15 to 20 per cent of hemothoraces seen in wounds of the thorax progressed to a chronic stage requiring operative treatment, whereas in civilian practice the incidence is more in the neighborhood of 5 to 10 per cent.

Whatever the incidence, the attitude toward significant bloody accumulations should be an aggressive one and every attempt made to evacuate the thorax completely and promptly. With such an approach the necessity of decortication diminishes and the re-establishment of pulmonary function is enhanced. With the addition of SK to his armamentarium the surgeon is offered additional means whereby the management of hemothorax may be accomplished effectively, as illustrated by the results obtained in these cases. Furthermore, when injuries and wounds of the chest occur in large numbers, as in war, the value of these agents will be increased. Striking as was the improvement in the treatment of wounds of the thorax in World War II, the use of streptokinase and streptodornase should lower materially the 15 to 20 per cent of cases of clotted hemothorax already referred to, and so reduce appreciably loss of man power.

REFERENCES

1. Tillett, W. S., and Sherry, Sol: The Effect in Patients of Streptococcal Fibrinolysin (Streptokinase) and Streptococcal Desoxyribonuclease on Fibrinous, Purulent, and Sanguineous Pleural Exudations, J. Clin. Investigation **28**: 173-190, 1949.
2. Tillett, W. S., and Garner, R. L.: The Fibrinolytic Activity of Hemolytic Streptococci, J. Exper. Med. **58**: 485, 1933.
3. Christensen, L. R.: Streptococcal Fibrinolysis: A Proteolytic Reaction Due to a Serum Enzyme Activated by Streptococcal Fibrinolysin, J. Gen. Physiol. **28**: 263, 1945.
4. Sherry, S., Tillett, W. S., and Christensen, L. R.: Presence and Significance of Desoxyribose Nucleoprotein in the Purulent Pleural Exudates of Patients, Proc. Soc. Exper. Biol. & Med. **68**: 179, 1948.
5. Tillett, W. S., Sherry, Sol, and Christensen, L. R.: Streptococcal Desoxyribonuclease: Significance in Lysis of Purulent Exudate, and Production by Strains of Hemolytic Streptococci, Proc. Soc. Exper. Biol. & Med. **68**: 184, 1948.
6. Tillett, W. S., Sherry, Sol, Christensen, L. R., Johnson, Alan J., and Hazlehurst, George: Streptococcal Enzymatic Débridement, Ann. Surg. **131**: 12, 1950.
7. Tillett, W. S., Sherry, Sol, Christensen, L. R., Johnson, Alan, and Hazlehurst, George: The Effect in Patients of Streptococcal Fibrinolysin (Streptokinase) and Streptococcal Desoxyribose Nuclease (Streptodornase), Tr. A. Am. Physicians **62**: 93, 1949.

8. Christensen, L. R.: Methods for Measuring the Activity of Components of the Streptococal Fibrinolytic System, and Streptococcal Desoxyribonuclease, J. Clin. Investigation **28:** 163, 1949.
9. Langston, H. T., and Tuttle, W. M.: The Pathology of Chronic Traumatic Hemothorax, J. THORACIC SURG. **16:** 99, 1947.
10. Unpublished observations.
11. Melick, D. W., and Spooner, M.: Experimental Hemothorax, J. THORACIC SURG. **14:** 461, 1945.
12. Tuttle, W. M., Langston, H. T., and Crowley, R. T.: The Treatment of Organizing Hemothorax by Pulmonary Decortication, J. THORACIC SURG. **16:** 117, 1947.
13. Samson, Paul C., Burford, Thomas H., Brewer, Lyman A., and Burbank, Benjamin J.: The Management of War Wounds of the Chest in a Base Center, J. THORACIC SURG. **15:** 1, 1946.

DISCUSSION

DR. E. I. EVANS, Richmond, Va.—We have heard a most scholarly presentation of what will prove to be, I believe, a classical discovery by Tillett and Sherry. I rise simply to add a small amount of emphasis to the presentation of Dr. Read and Dr. Berry; to present two cases, in one of which the results following the use of streptodornase were dramatic and, in the second, to indicate again that with every new preparation given us we have to keep an eye on the patient.

The first patient was a 17-year-old boy who suffered a gunshot wound of the chest about two months prior to coming to us. He came in with the physical appearance of a constricting hemothorax type of chest by all types of physical examination. He was slated for surgical decortication of the lung, and we prevailed upon Dr. Bigger to be allowed to try streptokinase on him.

(Slides.) This picture was taken with the patient lying down, Lipiodol instilled into the cavity. The empyema was infected by penicillin-resistant staphylococci. This shows the extent of the cavity which occupied practically the entire left thorax. He was given streptokinase in about the same manner indicated by Dr. Read for exactly twenty days. (Slide.) This shows the appearance of the cavity after six days' treatment. The next slide shows the cavity after twenty-one days' treatment with streptokinase-dornase solution and aspiration eight hours after each injection. The cavity has decreased to a space of only a very few cubic centimeters. The tube is being kept in place until we get practically no drainage. Clinically the boy is well and recovered without surgical decortication of the lung.

The next case is an 8-year-old child who had a small empyema of bloody type following some type of inflammatory pneumonia. Streptokinase-dornase was injected daily, with aspirations eight hours later, and on the sixth day Lipiodol was repeated; we are now confronted with a bronchopleural fistula. I am not sure that we enzymatically removed a covering over an healing bronchus, but this experience indicates that we must reserve final opinion on this treatment. We are impressed in other cases, about six in number (hemothorax following trauma), that streptokinase has been a valuable agent in liquefying a blood clot.

DR. BERRY.—I should like to make public acknowledgment of the generosity of Dr. Tillett and Dr. Sherry in allowing Dr. Read, who has been working with them over the past year, to use some of their own material they had gathered together for presentation. This phase of their work has been done in our chest service and they have been most generous in allowing us to use this outside our own confines whenever such has been necessary. These enzymes doubtless have many other possibilities besides their use in the chest and we have found them of great value on our general service also. I think that the work done here has already proved to us what a valuable agent or pair of agents these two enzymes are in the treatment of empyemas, whether tuberculosis or of pyogenic origin; they are of great help in cleaning them up. We have not yet determined, and Dr. Read may bring that up, what the effect may be upon the healing process, and when we think them safe we use it whenever one is caught in that unfortunate situation of empyema following any resectional work within the chest.

DR. H. A. BRODKIN, Newark, N. J.—I am grateful for the privilege of discussing this valuable paper. I regret that I was not aware that a paper on the subject of streptokinase

was to be read and thus failed to bring slides that would have illustrated the value of this agent in the successful conclusion of the following interesting case.

A 21-year-old Negro in the course of a routine chest x-ray examination was found to have a very extensive shadow which resembled a massive pericardial effusion. Numerous attempts at aspiration failed to yield any fluid. After a long period of observation and study, numerous clinicians came to the conclusion that the shadow represented an extremely thickened pericardium, or that the pericardial sac contained a very thick inspissated exudate or fluid. In order to make a definite diagnosis, and because of the possibility that this x-ray shadow might be a large mediastinal tumor, the left chest was explored. A huge, soft, solid tumor, which on microscopic section proved to be a thymoma, was dissected free from the anterior mediastinum. The tumor mass, which extended into both thoracic cavities, was bisected under the sternum. It was found to extend down over the left anterior mediastinum, left costophrenic angle to the vertebral column posteriorly. Its total weight was 1,280 grams. The mediastinum and pleural cavity were drained with two catheters attached to underwater drainage for two days.

Approximately a week later the right anterior chest was opened through an anterior fourth intercostal incision and a similar mass, more extensive, reaching around to the vertebral column on the right, was removed. This mass weighed 1,650 grams, thus making a total of almost 3,000 grams. One of the interesting findings was the presence of a large amount of black clotted blood that spread from underneath the sternum into the left chest, in spite of the drainage tubes. This was removed by means of ring forceps. Two large mushroom catheters attached to underwater drainage were placed into the anterior mediastinum and the right pleural cavity for four days. After the catheters were removed, postoperative films showed an extensive dense shadow which was assumed to be an accumulation of blood. Numerous attempts to aspirate it failed to yield any fluid. The shadow was then assumed to be clotted blood. Some streptokinase was obtained from Dr. Tillett's laboratory, and 10 c.c. were injected into this mass. Twenty-four hours later, aspiration into this mass yielded 500 c.c. of bloody fluid, and the roentgenogram showed almost entire clearing of the mass following aspiration. It was unnecessary to repeat this.

I am sure time will prove that we will owe a great debt to Dr. Tillett and the Bellevue group for furnishing us with this new and extremely valuable adjunct. With the proper use of this agent many surgical chest operations will be avoided.

DR. READ (closing).—I think what Dr. Brodkin brought out as to the usefulness of this material is true. This material is a tool to the surgeon and not the complete therapy in itself in any given situation. It cannot be placed into the chest and forgotten, but should be combined with other practical procedures in the management of the problem. Its action is self-terminating and repeated therapy and aspirations are often required. Its irritative qualities necessitate prompt aspiration within twelve to twenty-four hours, and successive aspirations thereafter. If this plan is not adhered to, exudative elements rich in fibrinogen pour into the area, and may lead to reloculation. With the procedures suggested these irritative effects are minimized, and the desired clinical effect is obtained.

With reference to the bronchopleural fistula: First of all, I think when it is used with the lung in place, in other words, not in a pneumonectomy site but in lobectomy or segmental resection, it is important that a tube should be in the area at the time. If any evidence of leakage or bronchopleural fistula is present, immediate suction is available. There have been two cases come to my attention which have had enzyme therapy following lobectomies, in which bronchopleural fistulas became manifest. As you all know, there is a tamponing effect of debris or fibrin so that a bronchopleural fistula may be dormant or occult. With the dissolution of the coagulum the fistula becomes manifest. This may be avoided in some instances by meticulous pleuralization of the bronchial stump at surgery.

There is no evidence in our studies that the enzymes create bronchopleural fistulas, but only that they make them apparent when they already exist. This is supported by laboratory evidence of complete lack of effect of these enzymes on living cells.

Finally, I should like to re-emphasize that this enzymatic therapy is only an adjunct to the complete management of the patient. For various reasons even decortication might at times be necessary. However, when properly used, it may serve as a very valuable agent in the management of hemothorax and empyema.

THE USE OF STREPTOKINASE-STREPTODORNASE IN THE TREATMENT OF HEMOTHORAX

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THIS article consists of a detailed report of the procedures used and the results obtained following the intrathoracic injections of partially purified streptococcal concentrates containing streptokinase and streptodornase* into patients with massive hemothorax. Previous publications have indicated both the development of the study and also the scope of the applicability of the streptococcal enzymatic substances as a therapeutic measure.[1-8]

The thoracic cases included in this article have been classified on the basis of whether or not the lung had been previously removed by operation or was still in situ. The presence of lung, collapsed by a coagulum, posed the problem of re-expansion and presented other special circumstances associated with the degree of organization of the fibrin, features which were not significant in the handling of the cases of postpneumonectomy hemothorax.

Additional groupings have consisted of cases referred to as *infected hemothorax*. This identification has been given to patients from whom the fluid derived by aspiration was thin and sanguineous rather than thick and purulent, but cultures were either positive prior to therapy or became so following dissolution of the loculated hemorrhagic coagulums.

From the standpoint of enzymatic action the chief basis for the differentiation between infected *hemothorax* and *empyema* is referable to the fact that in the former the principal solid constituent of the exudate is fibrinous against which streptokinase is primarily active, whereas in the latter group desoxyribose nucleoprotein is an additional important increment of the purulent exudate which requires the action of streptodornase.

The results obtained in patients with empyema are given in a separate article.[9]

The first 27 cases of hemothorax, treated with streptococcal enzymes by our group, constitute the substance of this report. They are divided as follows:

1. Sterile postpneumonectomy hemothorax—10 cases.
2. Infected postpneumonectomy hemothorax—4 cases.
3. Sterile hemothorax, traumatic, with lung in situ—11 cases.
4. Infected hemothorax, traumatic, with lung in situ—2 cases.

In assembling the data of each of the groups, the following patients previously reported upon have been included in this report.

Patient A. A. (Table I) was previously reported by Tillett and Sherry;[1] patients A. L. (Table I), H. F. (Table III) by Tillett, Sherry, Christensen,

From the Department of Medicine, New York University College of Medicine, and the Third Medical and Surgical Divisions of Bellevue Hospital (with special acknowledgments to the Chest Surgical Service, Dr. Frank Berry, Director).

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*Referred to as SK-SD.

Johnson, and Hazlehurst;[6, 7] patient D. McG. (Table II) by Tillett,[8] and was included in the presentation of Read and Berry made at the Thirtieth Annual Meeting of The American Association for Thoracic Surgeons. Their report is a separate communication in this JOURNAL.[10]

MATERIALS AND METHODS

Streptococcal concentrates containing streptokinase and streptodornase have been prepared by methods described by Christensen[11] and modified by Lederle Laboratories, Inc.* to meet practical problems encountered in the large scale production of active material.

Since in clotted hemothorax, fibrin constitutes the major substrate, streptokinase was the more important of the two enzymes employed. In several instances preparations rich only in streptokinase and containing very small amounts of streptodornase were used. These latter preparations were as successful in liquefying sanguineous coagulum as preparations rich also in streptodornase. From the standpoint of enzymatic activity, therefore, the quantitative data will center around the fibrinolytic reaction. However, since as a practical measure of manufacture, SD is usually incorporated in the finished product, the mixtures of SK-SD were used for injection into the patients.

The streptococcal concentrate was supplied in a lyophilized state under which conditions it was found to be sterile and stable. It is readily soluble in water or physiological saline but once put into solution, its potency begins to diminish. The practice has been adopted, therefore, of dissolving the contents of the ampule in physiological saline just prior to its actual introduction into the pleural space.

Dosage: Streptokinase.—The dosage of streptokinase per injection used in this study ranged from 80,000 units to 450,000 units per injection. Theoretically the unit dosage should bear a quantitative relationship to the amount of coagulum present in the thorax. However, since the latter cannot be measured accurately, varying amounts have been used for clinical trial. Doses above 100,000 units of streptokinase routinely set into motion large amounts of the fibrinolytic enzyme system whereas doses under 100,000 units in preliminary studies were not consistent in activating sufficient amounts of the fibrinolytic system for maximum effect in the thoracic area. Where estimations of the total amount of fluid and coagulum can be made, the maximum fibrinolytic systems can be expected to occur with titers of 100 to 500 units of streptokinase per cubic centimeter of chest fluid. For routine purposes in thoracic injections, ampules containing approximately 200,000 units of streptokinase have been regularly employed as a standard dose.

At present the enzyme concentrates used contain an inhibitor to streptokinase that is only of significance in highly concentrated solutions of the enzyme, and is of no significance in dilute solutions.

*Lederle Laboratories, Inc., Pearl River, N. Y., supplied the preparations used in this study.

Fig. 1 shows the results of an experiment designed to demonstrate this inhibition.* It will be noted from Fig. 1 that maximum speed of fibrinolysis occurred with a $\frac{1}{32}$ dilution of the original streptokinase solution.

From a practical standpoint of routine procedure, when a lyophilized ampule of streptokinase of 200,000 to 300,000 units is diluted up into approximately 50 c.c. of saline, or when the ampule is made up in a smaller volume of

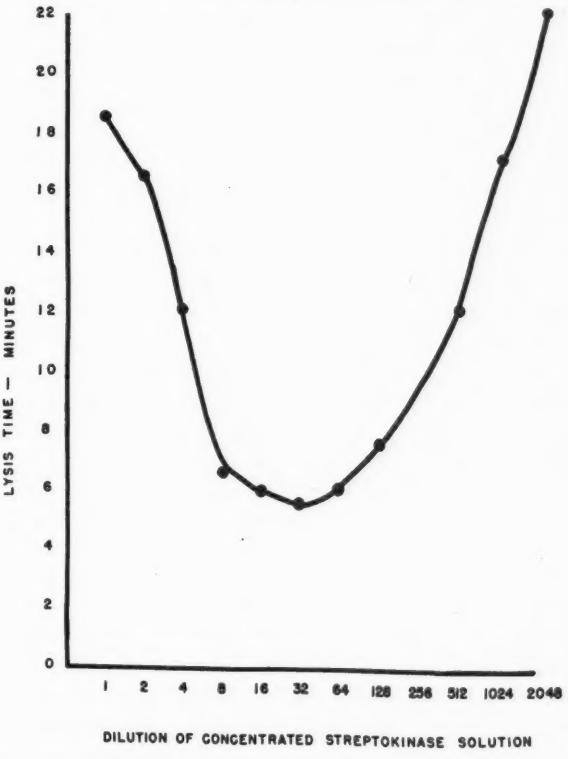


Fig. 1.—Demonstration of an inhibitor in a streptokinase preparation. Inhibition of fibrinolysis is evident at the highest concentrations of the streptokinase solution. Fibrinolysis is maximal at a $\frac{1}{32}$ dilution of the solution.

saline but injected into an area which has enough free fluid to dilute out the inhibitor, then the streptokinase will be maximally active. However, if one were to dilute up the whole dose in 1 to 2 c.c. of saline and inject it into the center of the coagulum in which no fluid was available to serve as diluent, little fibrin lysis would occur.

Two and possibly three types of inhibition of the fibrinolytic system are present in normal serum and in sanguineous exudates. One has been referred

*A purified streptococcal concentrate containing 300,000 units of streptokinase was dissolved in 10 c.c. of 0.01 M saline phosphate buffer at pH 7.4. To 0.1 c.c. of serial dilutions of this preparation was added 0.1 c.c. of a 1 per cent solution of Human Plasma Fraction III (source of serum increment), 0.1 c.c. of a $\frac{1}{5}$ dilution of Hemostatic Globulin (Lederle) (thrombin), and 0.9 c.c. of a 0.25 per cent Bovine Fibrinogen solution. Time of lysis of the resultant clot was measured.

to as trypsin inhibitor[2] and antifibrinolysin.[12] Our studies demonstrated its presence in a uniform amount in all specimens. Its action has not introduced difficulties in practical therapy. Whether or not the trypsin inhibitor and antifibrinolysin are the same or different substances remains to be determined.

A specific antibody to the streptococcal product has been described as occurring following both acute hemolytic streptococcal infections,[13] and the injections of SK.[2] Recognition of its presence is important only in patients who required protracted treatment. When present its inactivating effect has been overcome by increasing the dosage of SK one- or twofold.

Summary of Data Pertinent to Streptococcal Fibrinolysis in Relation to the Treatment of Patients.—All of the laboratory measurements previously described,[1, 2] which served as the experimental background in which the use of enzymatic therapy in patients was developed, are not regularly necessary for the practical and effective clinical application of streptokinase in treatment except for special instances.

However, for purposes of immediate reference, the increments involved in the fibrinolytic system and the mechanism of action are recapitulated in a brief review and are illustrated by the findings obtained from a case of clotted hemothorax presented in Fig. 2.

Streptokinase (SK) is elaborated extracellularly by hemolytic streptococci[14] and this product mediates and promotes the rapid alteration of fibrin and fibrinogen in an enzymatic system which requires the presence of a serum factor present in normal human blood.

The serum factor (lysing factor of Milstone,[15] plasminogen of Christensen and MacLeod,[16] and serum pro-fibrinolysin of Loomis[17]) occurs naturally in human blood in a stable but *inactive* form, and is referred to by us as the *activatable fibrin lysing system,* since it awaits the addition of streptokinase in order to exhibit the total qualities of active, rapidly acting, fibrinolysis and fibrinogenolysis. The *active fibrin lysing system,* when formed, is labile. The duration of its action, both in vitro, and in vivo, in patients, is self-terminating.

The patient A. Mc. (Fig. 2 and also Table I) was a 50-year-old white man who developed a loculated hemothorax following pneumonectomy for tuberculosis.

From the data of Fig. 2 note that the injection of streptokinase has rapidly activated large amounts of the active fibrin lysing system at the expense of the serum precursor (activatable fibrin lysing system) which was present in the exudate in an amount equal to that normally present in circulating blood. In our experience in the study of sanguineous exudates in patients, the active fibrin lysing which appears promptly following the introduction of the streptococcal product, has been demonstrable only *if and when free streptokinase is simultaneously present.* Furthermore, as long as free streptokinase is still demonstrable, continued activation of the fibrinolytic system proceeds, after the first period of activation, according to the extent to which there is a renewed influx locally of new serum increments. When, after the injection, free streptokinase is no longer present, the titer of activatable precursor rises to its previous

evel as supplied from the exudation of fresh serum and is available for the ubsequent development of more fibrinolytic activity. This latter point, there- ore, serves as an indicator for the appropriate time to administer the next lose of SK.

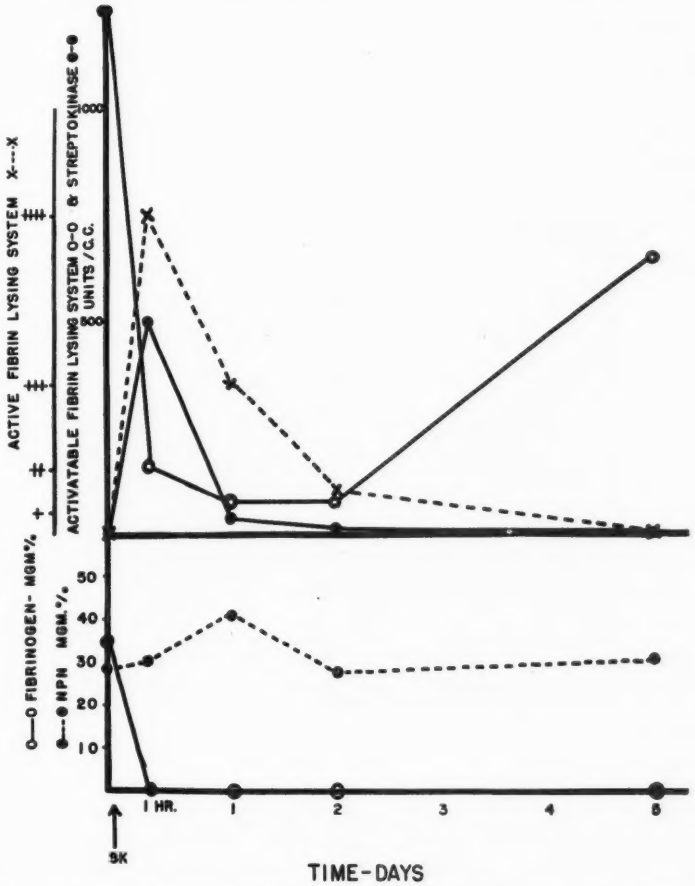


Fig. 2.—Summary of biochemical changes in chest fluid of patient A. Mc. (postpneumonectomy hemothorax) following the intrapleural administration of 300,000 units of streptokinase. Note the activation of the fibrin lysing system (*X—X*, upper graph) at the expense of the activatable precursor (*O—O*, upper graph), and the rapid fibrinogenolysis (*O—O*, lower graph) following the SK injection.

The significance of the serum increment in streptococcal fibrinolysis is ell illustrated in the following test, conducted in vitro, with material from patient.

Tube on the left (Fig. 3) contains a fibrinous mass suspended in 10 c.c. aline containing 10,000 units streptokinase and incubated at 37° C. for 4 ours. No lysis is noted. (The fibrinous mass was removed from the pleural

surface of a patient during decortication of a foul empyema.) The tube on the right contains a similar sized fibrinous mass, from the same patient, suspended in 10 c.c. serosanguineous fluid containing the normal amount of lysing factor to which 10,000 units streptokinase was added and incubated at 37° C. for 4 hours. Complete lysis of the fibrin has occurred. The serosanguineous fluid was removed by aspiration from the pleural cavity of a patient with hemothorax. The patient from whom the fibrinous specimen used in the preceding test was obtained had not been treated with SK-SD, nor was a sample of pleural effusion from this patient tested for serum lysing factor. Up to the present time a deficiency of the serum lysing factor in pretreatment samples of exudate has not been observed except in rare instances.

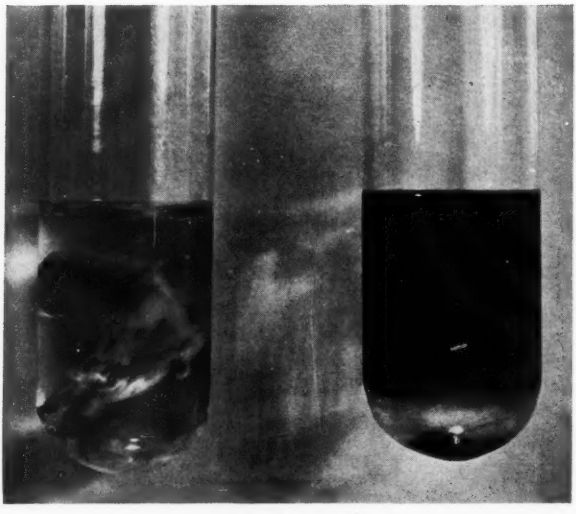


Fig. 3.—Demonstration of requirement of combination of streptokinase-serum factor to effect fibrinolysis (see text).

For practical purposes in following the course of events in the treatment of patients, and in association with clinical observations, determinations of the *active fibrin lysing system* present in the sanguineous exudate has proved to be the most useful of all the tests mentioned. It is performed as follows:

Active fibrin lysing system (equivalent to plasmin). To 0.1 c.c. samples of chest fluid are added 0.9 c.c. of 0.25 per cent Bovine Fibrinogen (Armour) in 0.01 M saline phosphate buffer (pH 7.4); 0.1 ml. of thrombin solution* is then rapidly added. The tubes are incubated in a water bath at 37° C; 0.1 ml. of saline instead of chest fluid is used as a control. The time of complete lysis of

*In the method originally described for active fibrin lysing system,[1] Lederle's Hemostatic Globulin was employed. This material is no longer available. Parke-Davis Bovine Thrombin containing 5,000 NIH units in a lyophilized ampule is now employed. (The ampule is diluted up in 50 c.c. of 50 per cent glycerol and stored in the icebox; 0.1 c.c. aliquots are employed for clotting test fibrinogen solutions.) However, this preparation contains a small amount of active fibrinolytic enzyme and has necessitated setting up different time standards relative to the control for expressing active fibrin lysing enzyme titers.

the fibrin clot is noted. In this method, the lysis of a standard fibrin clot by a fixed increment of body fluid is graded + to ++++, as follows:

Lysis up to 1 hour	++++
Lysis 1 to 3 hours	+++
Lysis 3 to 6 hours	++
Lysis 6 to 8 hours*	+
Control: 8 to 24 hours spontaneously	

This represents a practical method of expression of the concentration of the fibrin lysing enzyme. It is also of importance to note that whereas a unit of plasmin[2] is based on the liquefaction of a standard amount of fibrin in ten minutes, the estimations of the fibrin lysing system take into account the total time during which fibrinolysis is occurring. The significance of the time factor is not only important in in vitro studies but is obviously of special significance in gauging the utilization of SK in patients according to the principle of obtaining maximum effect from a single dose which may proceed as long as 24 hours.

An active fibrin lysing system should be present in significant amounts (at least ++) and demonstrable by this method for periods up to 24 hours following the intrapleural injections of streptokinase. This test need not be routinely employed but reserved for cases in which satisfactory fibrinolysis does not take place.

Method of Handling Individual Treatment.—Streptokinase, when injected, puts into operation immediately the process of fibrinolysis, which continues in the thorax for approximately 24 hours and then becomes self-terminating.

Although the streptokinase, when injected, immediately activates the fibrin lysing system, extensive lysis of the coagulum in the chest and the dissolution of fibrin loculation occur at variable periods of time depending on the physical form of the coagulum and the extent of contact between enzyme and substrate. (For discussion of this point see reference 8.) We have adopted a policy, therefore, of injecting the solution of SK and leaving it in situ for 12 to 24 hours before tapping the area again. After this period of time the complete removal of all fluid should be accomplished, by multiple thoracenteses if necessary (though the latter is rarely necessary). Extensive aspiration is of special importance because (1) it permits immediate radiographic examination to determine what has been accomplished as evidenced by changes in the x-ray shadow and increased expansion of the lung, and whether or not further therapy is necessary, (2) it removes from the chest residual irritants and pyrogens associated with the concentrates and the breakdown products of enzymatic digestion. If the lysed fluid is not aspirated, it not only prevents the expansion of the underlying lung, but may act as the site of new clotting and loculation when the enzyme action is finished, and new increments of fibrinogen enter from the pleural surface.

In an optimally successful situation following one injection, the complete coagulum is liquefied and removed within 24 hours by aspiration (usually 14 to 16 hours after SK). Further exudation of fluid due to the local irritating

*Or faster than control.

effect of the treatment usually appears in decreasing amounts over the next 24 to 48 hours and is removed by aspiration leaving the space clear. When fluid continues to exude in large amounts after this period of time, the reaccumulation has been found to be related to the underlying pathology rather than the use of the streptococcal enzymes.

Number of Treatments.—If complete liquefaction of the coagulum is not accomplished with the first injection, repeated injections may be indicated at 48-hour intervals, and should be continued until a maximum effect has been obtained. The routine procedure has been adopted, therefore, of administering SK on alternate days and draining by aspiration on alternate days.

The need for subsequent injections may be gauged by whether (a) a satisfactory clinical result has already been accomplished, (b) the fluid removed at aspiration has lost all its sanguinity and has been replaced by a thin serous fluid, (c) no more fluid can be obtained by aspiration.

Since streptokinase depletes the activatable fibrin lysing system in the chest fluid, subsequent injections of streptokinase do not set in motion as active a fibrin dissolving system as the initial injection. This may be a limiting factor in obtaining as extensive a fibrin dissolution on subsequent injections as occurs with the first injection, particularly if repetitions of treatment into large areas were to be given once or twice daily instead of at the spaced intervals described previously.

Toxicity.—The toxic reactions, described in detail in reference 8, are chiefly limited to a pyrogenic one and a local outpouring of serum and leucocytes. The febrile response, occurring in 60 to 70 per cent of cases, begins about 6 hours after the injection, reaches its peak (averaging 3° F.) in 24 hours, and subsides during the ensuing 24 to 48 hours. We have never observed it as a serious reaction, although it is our impression that febrile responses occur more frequently following the lysis of frankly hemorrhagic material than purulent exudates and may in part be referable to the absorption of hemoglobin. The administration of amidopyrine (0.1 Gm. three times daily) on the day preceding and the day of treatment has abolished the thermal reaction and abated considerably the symptomatology. Aspirin has proved useful but less successful than amidopyrine.

CLINICAL RESULTS

Group 1. Sterile Postpneumonectomy Hemothorax (10 cases).—Table I contains pertinent data with respect to the 10 patients of this group and Fig. 4 illustrates by x-ray photographs the extensive liquefaction and removal of the previously loculated coagulum within 24 hours of the instillation of SK.

Comment: It is not the purpose of this article to discuss or recommend the total management of cases of pneumonectomy that may have varying amounts of postoperative bleeding and may present varying surgical anatomical situations that require individualized treatment to obtain optimum objectives after the lung has been removed. The effectiveness of enzymatic fibrinolysis in the cases of Group 1 has been unusually uniform both in the completeness with

TABLE I. CASES OF GROUP 1: UNINFECTED POSTPNEUMONECTOMY HEMOTHORAX*

PATIENT	AGE IN YEARS (SEX)	OPERATION	DURATION PRIOR TO SK (DAYS)	AMT. OF FL. ASP. JUST PRIOR TO SK (C.C.)	AMT. OF FL. ASP. WITHIN 24 HOURS POST SK (C.C.)	TOTAL FL. ASP. POST SK (C.C.)	NUMBER DAYS POST SK ASP.†	SUBSEQUENT COURSE
A. A.	20 (M)	Pneumonectomy for bronchiectasis	29	2	1,100	1,800	12	Febrile course subsided post SK. Thoracoplasty 3 weeks later
H. S.	40 (M)	Pleuropneumonectomy for lung abscess, chronic empyema	14	30	950	1,025	5	Bronchopleural fistula opened and spontaneously closed. Thoracoplasty 18 days later (see text)
A. Mc.	46 (M)	Pleuropneumonectomy for tbc.	17	2	800	1,250	5	Thoracoplasty 4 weeks later
A. L.	31 (F)	Pleuropneumonectomy for tbc.	27	50	650	1,075	8	Thoracoplasty 17 days later. Patient succumbed to pulmonary edema on operative day
F. M.	33 (M)	Pleuropneumonectomy for tbc.	34	30	400	700	3	Thoracoplasty 2 weeks later
M. G.	34 (M)	Pleuropneumonectomy for tbc.	37	0	190	190	1	Tube drainage. Thoracoplasty 3½ weeks later
L. H.	29 (M)	Pleuropneumonectomy for tbc.	40	30	750	1,100	4	Thoracoplasty 3 weeks later
F. B.	34 (F)	Pneumonectomy for tbc.	20	25	450	1,230	8	Thoracoplasty 26 days later. Toxic reaction to SK (fever, vomiting)
R. P.	48 (M)	Pneumonectomy for tbc	16	15	900	1,450	5	Thoracoplasty 3 weeks later
M. W.	44 (M)	Pneumonectomy for tbc.	14	10	350	550	3	Thoracoplasty 10 days later

*Each patient received 1 injection of SK except Pt. A.A. who received 3 (see text).
†Indicates in days, time over which aspirations were required following fibrinolysis by SK.

which liquefaction has been accomplished with a single injection and in the rapidity with which the desired result has been obtained. The consistent success in the fibrinolytic aspects of the treatment of this type of massive postpneumonectomy hemothorax is referable to the particularly favorable conditions which exist. The thoracic cage serves as a fixed closed "container" for the fibrin deposits and permits the introduction of solutions of SK under particularly favorable conditions of maximum and sustained contact between enzymatic system and its substrate.

The practical point continually arises in this group of patients, as well as in others with massive extravascular hemorrhagic deposits, concerning the time during the postoperative hemorrhagic period at which SK treatment should be instituted. As indicated in Table I, the postoperative day of injections of SK ranged from the fourteenth to the fortieth. In our series the factor which served as an indication for the use of SK was the increasing formation of coagulum that was not amenable to removal by aspiration. The application of lytic therapy too soon after operation might presumably lead to more bleeding by reopening thinly thrombosed vessels. We have up to the present time never observed this complication but it will be subsequently discussed in more detail. Another possible difficulty arising from the application of SK too early postoperatively involves the opening of the bronchus of the pulmonary stump that has not been adequately pleuralized.

A bronchopleural fistula developed in patient H. S. (Table I and *C* and *D* of Fig. 4). The opening was first demonstrable 4 hours after the introduction of 200,000 units of SK, but closed 24 hours later without evidence of the development of contaminating infection of the pleura. The fistula reappeared 18 days later at the time of thoracoplasty and remained open until a suture observed by bronchoscopy was removed. The fistula then closed promptly and drainage ceased spontaneously. A separate report to be subsequently published will deal with our experience in cases of bronchopleural fistulas, which require special consideration because of the contraindication to the use of SK which may exist.

At the other extreme of the timing of the postoperative use of SK, prolonged delay will render the application of the enzyme ineffective if organization has occurred through the completion of fibrotic cellular infiltration of the coagulum. In our experience this difficulty has not been encountered in the cases of postpneumonectomy. For example, patient L. H. (Table I) received successful lytic therapy 40 days postoperatively. However, as will be discussed later, the time factor in relation to organization of tissues appears to be important in patients with hemothorax in whom the lung is in situ.

The *dosage* of SK in the patients of Group 1 consisted of 100,000 to 400,000 units contained in 20 c.c. of sterile physiological salt solution. A single injection was adequate in the treatment of 9 of the patients. Patient A. A. (Table I) received three injections, two of which were primarily for investigational rather than therapeutic purposes. The sharp increase in the amount of fluid obtained by aspiration during the first 24-hour period after the introduction of SK has regularly been a striking characteristic of the effect of the enzymatic solutions, and is evident from the quantitative data given in Table I. The

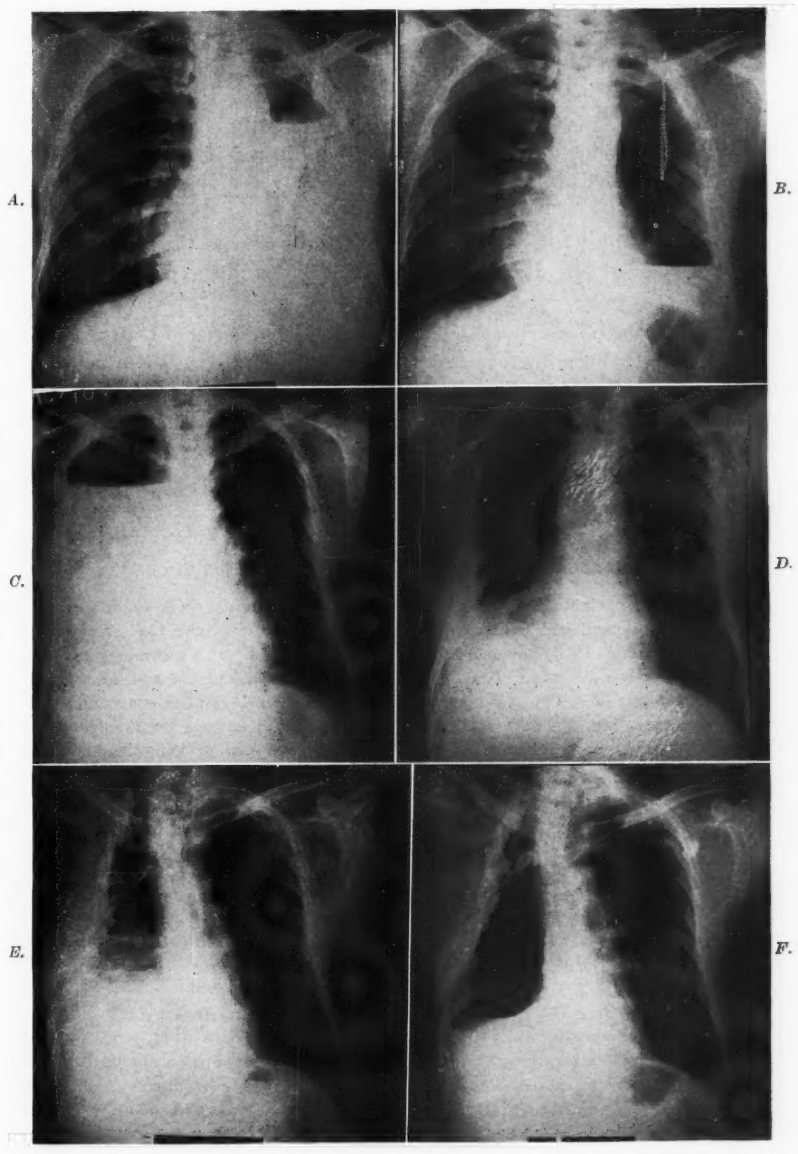


Fig. 4.—Extensive removal of loculated thoracic coagulum, following streptokinase therapy, in three patients with postpneumonectomy hemothorax. *A*, Case L. H., prestreptokinase. *B*, Case L. H., 24 hours poststreptokinase. *C*, Case H. S., prestreptokinase. *D*, Case H. S., 24 hours poststreptokinase. *E*, Case A. Mc., prestreptokinase. *F*, Case A. Mc., 72 hours poststreptokinase.

increase is accounted for by the liquefying process itself supplemented by an outpouring of additional serous material referable to the local irritation.

The subsequent post SK aspirations (Table I) indicate the time required to empty the residual content as an expression of the successful termination of the fibrinolytic purposes of the therapy. In each of the cases of Group 1 thoracoplasty was subsequently performed successfully. In an additional case of our series, previously reported,[8] a marked contralateral mediastinal shift was rapidly rectified following liquefaction and removal of postoperative collections of fluid.

The photographic illustrations in Fig. 4 demonstrate the thoroughness of the lytic action of SK in making possible the ready removal of massive coagulums.

Group 2. Infected Postpneumonectomy Hemothorax (4 cases).—These patients (Table II) have been included in a group referred to as infected hemothorax rather than empyema because, as previously mentioned, at the time they were presented for enzymatic therapy the character of the exudate was that of hemorrhagic coagulum rather than that of purulent infection.

In 1 of the patients (J. H.), cultures of pretreatment samples of the sanguineous fluid obtained by aspiration were positive. In patients R. S., D. McG., and J. R., however, the contaminating organism was recovered only after lysis had been accomplished.

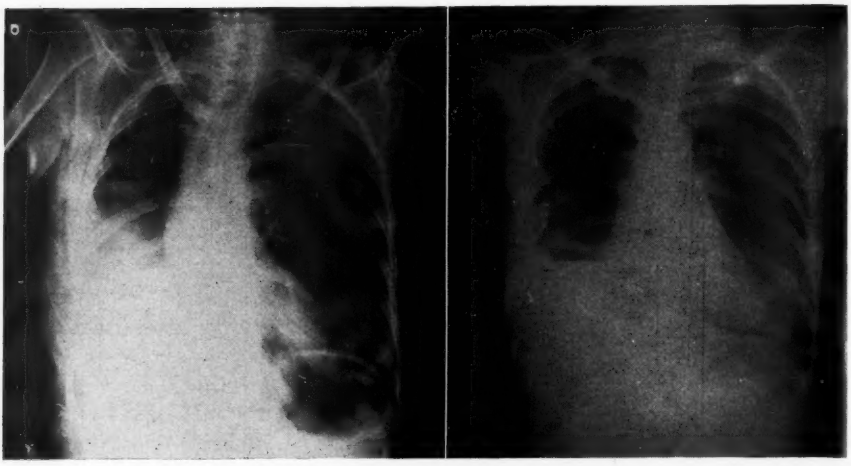
The details of patient R. S. (Fig. 5) are as follows: 57-year-old white woman with chronic lung abscess and suppurative disease of the right lung who had a lobectomy in October, 1949, followed by a pneumonectomy on Feb. 1, 1950. The pathology of the lung removed was described as suppurative bronchiectasis. The patient did well in the immediate postoperative period. The right thorax filled up with a loculated coagulum. On the tenth postoperative day the patient became febrile. Thoracenteses on the eleventh and twelfth postoperative days yielded only 150 c.c. and 100 c.c. of sanguineous fluid, respectively, which were sterile on culture. X-ray examination at this time still revealed an extensive coagulum (Fig. 5). On the thirteenth postoperative day a total of 390,000 units SK and 3,000 units SD were injected intrapleurally in three sites. The next day 1,200 c.c. of thin bloody fluid were removed and the thorax emptied of its coagulum by x-ray examination. Culture of this fluid revealed *Aerobacter aerogenes.* The patient was immediately placed on chloramphenicol per os (2 Gm. every day). Four days later the thorax was again injected with 200,000 units SK and 60,000 units SD in 25 c.c. of a ½ per cent solution of chloramphenicol. By the next day the pleural fluid was sterilized and the infection eradicated. The temperature fell and the subsequent course including thoracoplasty was uneventful. Fig. 5 also graphically summarizes the course of events in this patient.

Patient J. R. (Table II) ran an interesting course characterized by the development of a spiking fever following liquefaction with a single dose of SK-SD (250,000 units). Furthermore, the material aspirated after lysis was positive for tubercle bacilli whereas previous ones had been sterile. Streptomycin therapy was introduced and the fever subsided in 8 days. Cultures of serous exudate which reformed after the primary evacuation were sterile. After an interval of 3 months a thoracoplasty was successfully performed without drainage. There has been an uneventful 2-year follow-up of patient J. R.

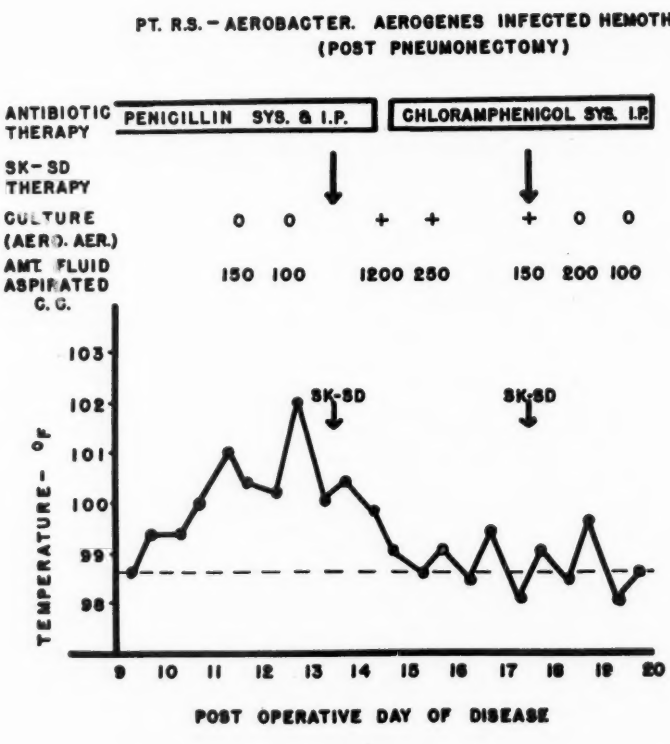
Patient J. H. (Table II) (previously reported[6]) was an interesting and instructive example of the capacity for sterilization induced by enzymatic clearing. The intrathoracic coagulum contained *Bacillus pyocyaneus* which, over an extended period of time, was un

TABLE II. CASES OF GROUP 2: INFECTED POSTPNEUMONECTOMY HEMOTHORAX

PATIENT	AGE IN YEARS (SEX)	OPERATION (PNEUMONECTOMY FOR)	BACTERIOLOGY	DURATION PRIOR TO SK (DAYS)	AMT. OF FL. ASP. JUST PRIOR TO SK (C.C.)	NUMBER OF INJECTIONS OF SK	TOTAL FL. ASP. POST SK (C.C.) (DAYS OF ASP.)	ANTIBIOTIC	SUBSEQUENT COURSE
D. McG.	62 (M)	Ca. of lung	*Bacterium coli*	45	10	4	2,000 (21 days)	Chloromycetin, streptomycin	Sterile and afebrile in 12 days; thoracoplasty without drainage
R. S.	59 (F)	Chronic suppurative disease	*Aerobacter aerogenes*	13	100	2	1,800 (7 days)	Chloromycetin	Sterile and afebrile in 5 days; thoracoplasty without drainage
J. H.	62 (M)	Chronic lung abscess	*Bacillus pyocyaneus*	30	30	5	1,570	None (see text)	Sterile and afebrile in 6 days, thoracoplasty without drainage
J. R.	14 (M)	Tbc.	Tbc.	32	3	1	1,700 (17 days)	Streptomycin	Afebrile in 8 days; thoracoplasty without drainage



A. *B.*



C.

Fig. 5.—Case R. S. Removal of loculated coagulum and sterilization of area in a case of infected postpneumonectomy hemothorax. *A*, prestreptokinase. *B*, 24 hours poststreptokinase. *C*, Graphic summary of clinical course.

affected by numerous antibiotic and antiseptic reagents introduced locally. However, following three injections of SK-SD on alternate days, followed by alternate days of drainage, sterilization was accomplished. This sequence of events has been repeatedly observed in other types of refractory infections. The principles involved have been extensively discussed in reference 8.

Comment: Effective lysis was accomplished in the 4 patients of Group 2 as in those of Group 1. However, the presence of viable bacteria introduced a second objective to treatment in addition to the mechanical liquefaction of fibrin.

That the action of the enzymes previously referred to as streptococcal enzymatic débridement[6] has in some instances been followed by the sterilization of areas of chronic refractory infection has been described and discussed.[8]

It has also been made clear that the advantageous use of antibiotic therapy has been enhanced by the local enzymatic cleaning process.

Patients D. McG., R. S., and J. R. received antimicrobial therapy during and, for varying periods of time, after instillation of SK.

The exudates, although thin and sanguineous before therapy, became thicker and more cellular as the injections proceeded. The change was due in part to the cellular outpouring associated with the irritative action of the enzymes and perhaps also to a transient pleuritis set up by the bacteria released from the interior of the coagulum.

Aspirations over a greater number of days were required for Group 2 than for Group 1, although the end result with final successful thoracoplasty was the same in both groups.

Group 3. Uninfected Hemothorax With Lung In Situ (11 cases).—The cases included in Groups 3 and 4 were primarily of traumatic origin. The data of Table III were assembled in order to consolidate special points. However, there were considerable differences in the conditions presented by the several patients that altered the methods of enzymatic therapy and influenced the final results.

The detailed reports of 3 cases are, therefore, presented which illustrate the types of problems and the practical methods that were employed in attaining ultimate enzymatic eradication of the widespread fibrin deposits.

Patient J. W., hemothorax following bullet wound (Fig. 6).—J. W., a 24-year-old Negro man, was shot in the left chest during an attempted robbery. The bullet entered the seventh intercostal space in the posterior axillary line and lodged posteriorly at about the level of the first thoracic vertebra. The patient entered the hospital in shock, dyspneic and coughing up blood. There was evidence of subcutaneous emphysema over the wound, and signs of fluid in the left chest. X-ray examination revealed a hydropneumothorax on the left, with atelectasis of the left lower lobe.

The hemoptysis stopped spontaneously within 24 hours of admission. The patient was placed on large doses of penicillin. Thoracentesis was attempted without success. On the eighth day of illness another thoracentesis yielded only 33 c.c. of sanguineous fluid, and a subsequent tap was completely unsuccessful. By the eighteenth day, x-ray examination still revealed a considerable coagulum at the left base with some thickening of the interlobar fissure (Fig. 6).

TABLE III. CASES OF GROUP 3. UNINFECTED TRAUMATIC HEMOTHORAX (LUNG IN SITU)

PATIENT	AGE IN YEARS (SEX)	TYPE OF TRAUMA	DURATION PRIOR TO SK (DAYS)	AMT. FL. ASP. JUST PRIOR TO SK (C.C.)	NO. INJ. OF SK (M, MULTIPLE) (S, SINGLE)*	AMT. FL. ASP. WITHIN 24 HOURS OF SK (C.C.)	TOTAL FL. ASP. POST SK (C.C.) (DAYS OF ASP.)	ESTIMATION OF PLEURAL CLEARING (SEE TEXT)†
P. R.	47 (M)	Bullet wound	14	25	2 (M)	850	2,700 (18)	Partial
J. W.	24 (M)	Bullet wound	19	100	1 (S)	600	600 (1)	Extensive
W. R.	24 (M)	Bullet wound	11	350	1 (S)	300	300 (1)	Extensive
E. S.	29 (M)	Stab wound	31	1	1 (S)	215	215 (1)	None
W. S.	20 (M)	Stab wound	8	2	1 (S)	100	200 (2)	None
T. C.	31 (M)	Stab wound	10	30	2 (M)	300	1,080 (6)	Moderate
H. F.	52 (M)	Fractured ribs	22	2	1 (M)	400	Drainage bottle (3)	Extensive
J. F.	63 (F)	Fractured ribs	26	400	1 (S)	400	650 (4)	Extensive
C. McD.	53 (M)	Fractured ribs	22	100	1(M), 1(S)	680	1,850 (8)	Extensive
C. B.	36 (F)	Sympathectomy, second stage	23	50	2 (S)	250	725 (6)	Extensive
S. McK.	37 (M)	Vagotomy	2	0	1(M), 2(S)	710	1,810 (4)	Extensive

*M signifies simultaneous injection into multiple sites. *S* signifies that total dose was introduced into a single site.

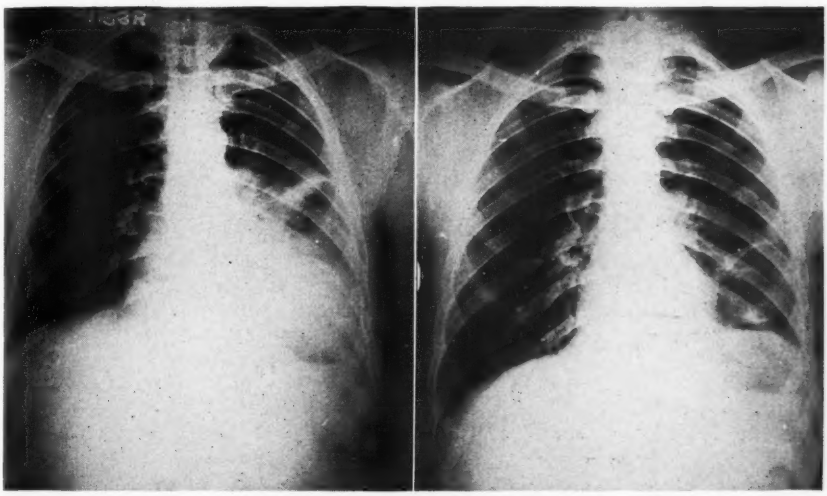
†Indicates prompt effect directly referable to action of SK.

On the nineteenth day the patient was tapped, a small amount of bloody fluid aspirated, and 240,000 units of streptokinase injected. The next day over 600 c.c. of sanguineous fluid were removed with ease. After this there was rapid clearing of the area. Fig. 6 was taken approximately 10 days after the use of streptokinase and reveals only a small amount of interlobar thickening remaining. The patient was then discharged to stand trial.

Patient C. B., hemothorax following sympathectomy (Fig. 7).—C. B., a 36-year-old colored woman, entered Bellevue Hospital on Dec. 27, 1948, for her second stage sympathectomy for severe essential hypertension. Surgery was performed on Dec. 29, 1948. Postoperatively the patient developed a hemothorax on the left. Thoracentesis yielded 750 c.c. and 150 c.c., respectively, on the fifth and sixth postoperative days, but subsequent taps were unsuccessful. X-ray examination (Fig. 7) on the twenty-second postoperative day revealed a posterolateral density in the left chest. The patient was injected on two occasions (twenty-third and twenty-ninth postoperative days) with 80,000 units of streptokinase. As a result of the streptokinase, 800 c.c. of sanguineous fluid were removed by thoracentesis with extensive clearing by x-ray examination (Fig. 7). The patient was discharged on the forty-ninth postoperative day, 20 days after the streptokinase therapy.

Patient C. McD., hemothorax due to fractured ribs (Fig. 8).—C. McD., a 53-year-old alcoholic white man, fell down a flight of stairs and sustained fractures of the right frontal bone, nasal bones, outer one-third right clavicle, and multiple fractures of the third to the eleventh ribs on the right. The patient was desperately ill and required transfusions, nasal oxygen, antibiotic, and frequent tracheobronchial suction during the first week of his illness. X-ray examination revealed a hemopneumothorax of considerable ex-

tent on the right. By the twenty-fourth hospital day, the patient's general condition had improved considerably but only 250 c.c. of fluid had been previously obtained by two thoracenteses. X-ray films revealed an extensive loculated coagulum in the right chest (Fig. 8, *A*); 240,000 units of SK were injected into the posterior chest and 120,000 units in the mid-axilla; 1,000 c.c. of fluid were removed in the next forty-eight hours with considerable clearing over the posterior chest. However, there was still considerable coagulum in the lower right anterior chest (Fig. 8, *B*). The patient was tapped anteriorly in the fourth interspace just lateral to the nipple, and 240,000 units SK injected intrapleurally. Over the next 48 hours 770 c.c. of fluid were removed from that area. X-ray films now revealed (Fig. 8, *C*) much further clearing and the physical signs of fluid were no longer present. The patient was mobilized, started on deep breathing exercises, and discharged to the clinic. Follow-up x-ray studies (Fig. 8, *D*) 2 months later showed almost complete clearing of the residual density.



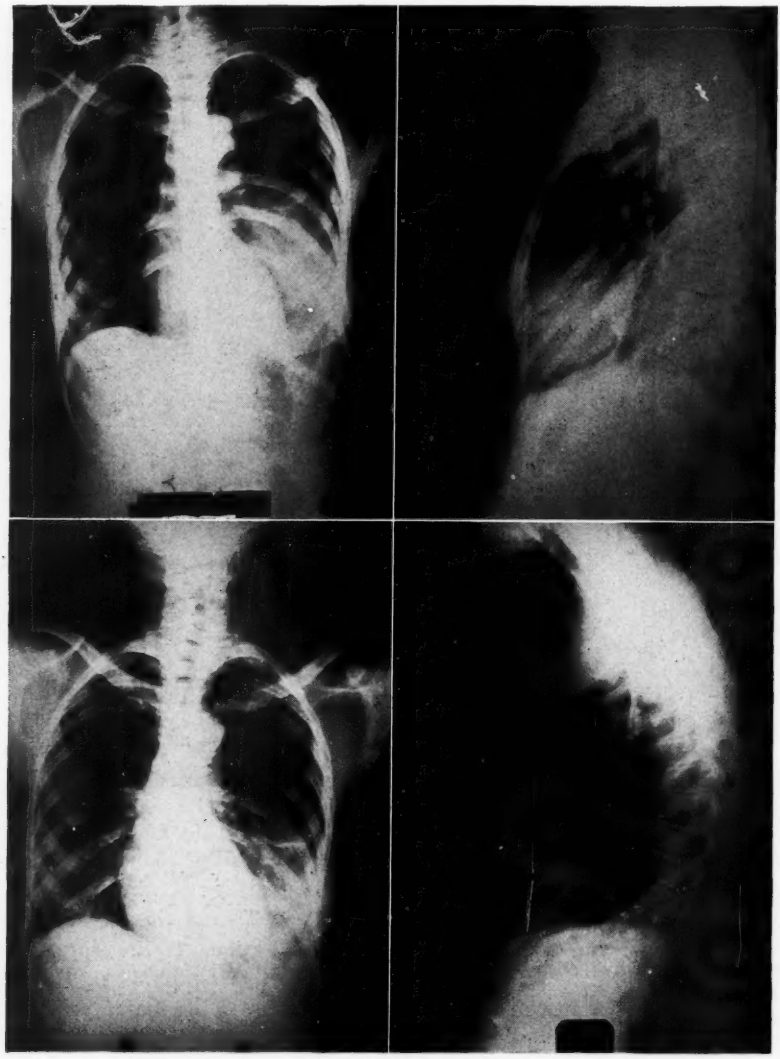
A. *B.*

Fig. 6.—Case J. W. Hemothorax following bullet wound. *A*, eighteenth day posttrauma and just prior to streptokinase therapy. *B*, 10 days poststreptokinase therapy.

None of the cases of this group came to decortication and all resolved completely. In 9 of the cases there was extensive lysis of coagulum by injections of streptokinase with removal of large quantities of sanguineous fluid and complete expansion of the underlying lung. Two of these 9 cases were handled by tube drainage, the rest by needle aspiration. In the other 2 cases (E. S. and W. S.) little effect could be attributed to streptokinase. However, in both these cases previous aspirations had removed the major part of the blood since the underlying lung had been almost completely expanded. After streptokinase, small amounts of serous fluid were removed indicating the absence of any sanguineous coagulum. Little immediate effect was noted on the x-ray density, and it is presumed the latter probably represented pleural reaction or complete cellular organization.

Comment: In general the results described in Group 3 have been considered very good but variable when compared to the uniformity of the effectiveness in the cases of postpneumonectomy hemothorax. This is to be expected

A.



B.

Fig. 7.—Case C. B. Hemothorax following sympathectomy. *A*, Posteroanterior and lateral views on twenty-second postoperative day and immediately prior to streptokinase therapy. Note large hematoma in posterolateral area of left chest. *B*, Posteroanterior and lateral views ten days poststreptokinase therapy. Although some density still remains, extensive clearing is noted on the lateral view.

when recognition is given to the differences existing in the presenting conditions. The hemothorax following pneumonectomy resulted from the slow progressive ooze of serosanguineous fluid into a large thoracic space. Under

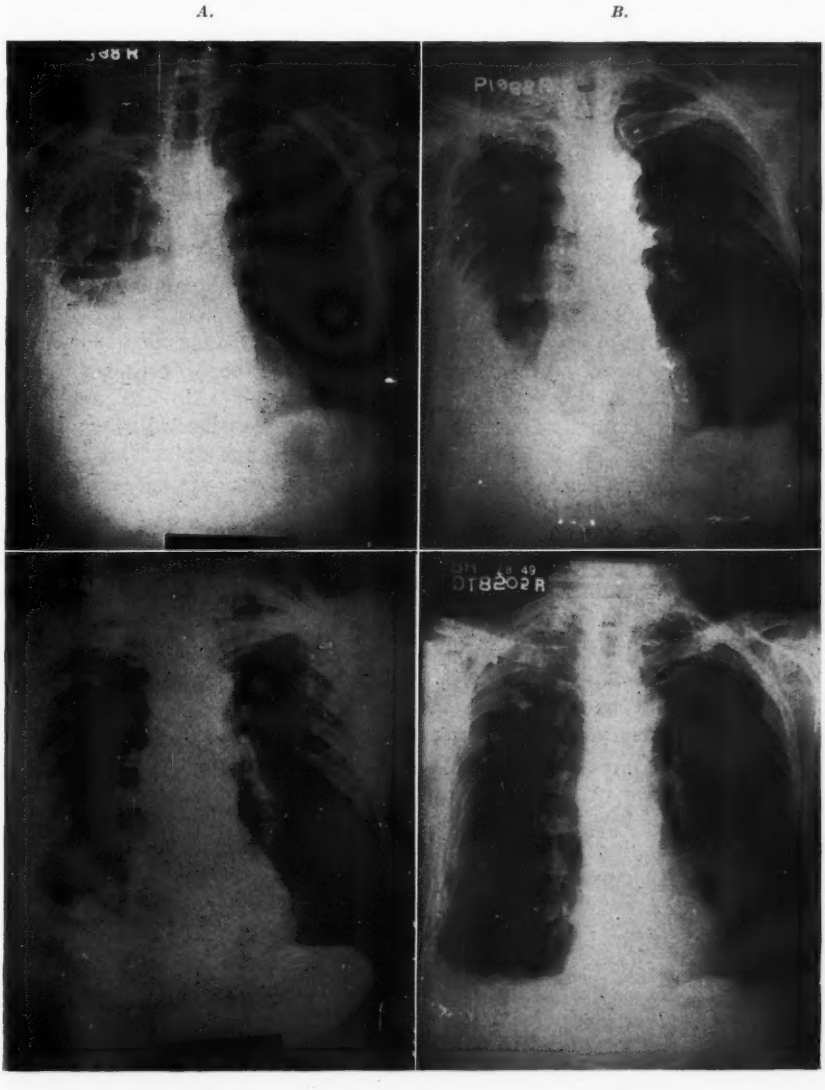


Fig. 8.—Case C. McD. Hemothorax due to fractured ribs. *A*, Appearance on twenty-fourth day posttrauma and immediately prior to SK therapy. *B*, Appearance 48 hours post first SK treatment. *C*, Appearance 48 hours post second SK treatment. *D*, Appearance at follow-up, 2 months post SK therapy.

these circumstances the clot forms gradually and is a meshwork of fluid and fibrin. Organization can begin only from the sole remaining parietal pleura and cannot be expected to bridge across the thorax for a considerable period of time.

In the cases in which hemorrhage occurred into the intact lung-containing thorax, the bleeding, arising from trauma or postoperatively, was usually gross in amount and rapid in rate of initial accumulation. The exudate, being essentially whole blood, is at first rich in fibrinogen and the coagulum formed is liable to be composed chiefly of fibrin. If the lung is still mobile, defibrination may take place with widespread coating of the pleural surfaces with a dense fibrin layer.[18] Melick and Spooner[19] have described the reaction that is evident in the two layers of pleura and have observed that organization begins early from both surfaces and may be completed early according to the closeness of the approximation of visceral and parietal pleura. When extensive pneumothorax has been present together with hemothorax (Patient H. F., Table III), the situation more closely simulates that present in the postpneumonectomy cases, since the collapsed state of the lung causes a wide separation of the visceral and parietal pleural surfaces.

In view, therefore, of our actual experience together with the special conditions inherent in traumatic hemothorax, the principles and practical methods of applying therapy may be outlined as follows:

1. *Institution of SK instillations early following the initial gross hemorrhagic episode but after bleeding has essentially ceased.*

With the exception of S. McK. (Table III) the patients of Group 3 were available for SK therapy *only after* repeated, and often daily, efforts at aspiration by thoracentesis had begun to yield smaller amounts of fluid even though the thoracic shadow seen on x-ray examination remained extensive and the lungs were compressed.

The recommendation of early aggressive treatment as soon as bleeding has spontaneously stopped raises the question, mentioned previously in this article, of whether or not SK will cause recurrence of fresh bleeding. Since the action of SK is a local surface one, it is deemed unlikely that its contact with the one small end of intravascular thrombus would effect its complete liquefaction. In our experience the theoretical improbabilities have been in consonance with actual experience.

Patient S. McK. (Table II) received an injection of SK on the second postoperative day without any fresh bleeding. We have information of 3 other patients at other institutions injected within 48 to 72 hours of the intrapleural bleeding episode without recurrence of hemorrhage.

Patient E. S. (Table III) may be cited as an example of an unsatisfactory result which seems to have been referable to the fact that SK therapy was deferred until the thirty-first posttraumatic day. No liquefying effect was demonstrable either by changes in the character of the fluid or by prompt alterations in the x-ray shadow. It is reasonable to presume that extensive cellular organization had occurred.

2. *Requirements for:* (a) *multiple injections simultaneously into several different sites and* (b) *repeated injections.*

On considering the problems presented by hemothorax with the lung in situ, as experience has accumulated, the value of introducing SK into several different sites at the time of beginning treatment has become evident.

The anatomic situation existing in traumatic hemothorax often consists of an extensive plastering of the pleural surface extending from the extreme posterior limits to the anterior mediastinal area. The extent of the diffusion of the enzyme from a single site contained in 20 c.c. of fluid may be restricted. Since, therefore, lytic action depends on direct contact between enzyme and substrate it is apparent that material placed in the posterior area, for example, may not extend throughout the total pleural area.

In considering the total practical management of patients with massive traumatic hemothorax, the objective is to obtain maximum pulmonary expansion in as short a time as possible. In this connection it is important to recognize the fact that streptokinase serves solely as a reagent which under appropriate conditions causes the transformation of the solid coagulum to a thin solution. Once this effect has been accomplished, the subsequent management of the case, in evacuating thoroughly the pleural contents requires consideration of factors such as desirability of using only intercostal thoracenteses, or closed drainage through a thoracotomy tube with or without negative pressure.

In some instances—not reported in this article—small tears of the lung have previously existed through which positive intrapleural pressure has developed. Similar situations have occurred following SK in postlobectomy cases. In the treatment of cases under these conditions, lysis of clot with SK has been followed immediately by closed tube drainage under water seal and suction has been applied. The pulmonary leaks have closed promptly and improved expansion has been accomplished.

In attempting to arrive at uniformity in the details of the treatment of hemothorax with the lungs in situ, it is obvious that a larger experience with well-studied cases is required. However, that physical changes in the solid fibrin have been effected by fibrinolysis in the patients of Group 3 has been demonstrated.

In attempting to summarize the final results in the cases of Group 3, it has been difficult to measure quantitatively the extent and speed of clearing of the involved pleural area in relation to results that might have been derived from other procedures or from permitting spontaneous absorption to occur.

In spite of this difficulty the following appraisal is offered:

Prompt and extensive clearing of pleural x-ray shadow in 9 of 11 cases.
No effect in 2 cases.

For purposes of completeness in presenting the details of the 10 patients, a brief description of the immediate effects and subsequent course of each is now included.

	IMMEDIATE EFFECT	SUBSEQUENT COURSE
J. W.	Extensive clearing	Discharged 3 weeks post SK with excellent radiographic result.
W. R.	Extensive clearing	Discharged 5 days post-treatment at which time small residual density was continuing to clear.
P. R.	Considerable clearing over upper two-thirds of thorax; residual density in interlobar fissure and at right base.	Almost complete spontaneous resolution of residual density in 5-week period post SK; discharged home.
E. S.	No significant changes noted.	Patient had been previously surgically explored for lacerated lung. At time of injection only straw colored fluid obtained. Extensive clearing occurred spontaneously over subsequent 6 to 8 weeks. X-ray shadow probably pleural and not true coagulum.
W. S.	No significant changes noted.	Patient complicated with prolonged high fever. Only serous fluid obtained after SK. Little effect attributable to SK. Slow clearing spontaneously. Discharged 21 days after SK. No follow-up. Lack of response to SK may be due to pulmonary pathology rather than presence of a coagulum.
T. C.	Extensive clearing over right lower chest posteriorly; moderate clearing over right lower chest anteriorly.	Clinical course complicated by right upper lobe pneumonitis which cleared rapidly with penicillin therapy. Patient discharged 3½ weeks post SK therapy with spontaneous clearing of residual pleural thickening in the region of the diaphragm.
H. F.	Marked expansion of previously collapsed lung, and extensive clearing.	Thoracotomy tube alone had failed in this hemopneumothorax. With SK, coagulum and air evacuated rapidly. Lung completely expanded. Residual density spontaneously cleared. Patient discharged 2 months post SK.
J. F.	Extensive clearing over site of previous shadow with complete expansion of lung. Some residual density anteriorly adjacent to pericardium.	Patient originally considered for decortication by surgeons but severe hypertensive cardiovascular disease contraindicated procedure. Complete spontaneous resolution of small residual density occurred over a 4-week period after SK.
C. McD.	Extensive clearing of multiloculated coagulum. Lung completely expanded. Moderate residual density at site of rib fracture.	Patient complicated by skull fracture and general debility. Surgery contraindicated. Clinical improvement marked after SK therapy. Progressive and complete spontaneous resorption of residual density over subsequent 2 months.
C. B.	Marked clearing over site of previous density.	Small residual density spontaneously cleared over next 2 months.
S. McK.	Good clearing over upper two-thirds of site of disease. Residual density at base.	Although rest of left pulmonary field cleared completely, the density at base remained. This has been identified as an atelectatic left lower lobe, presumably related to the original surgical procedure.

Group 4. Infected Hemothorax With Lung in Situ.—Since the SK treatment of the 2 patients of this group followed the principles previously discussed but varied according to individual condition each may be briefly described as follows without tabulated data:

Patient B. L., white man, 28 years of age, received a bullet wound in the left thorax (Fig. 9). He became available for SK treatment on the thirty-third posttraumatic day, at a time when there had been little or no change in the x-ray shadow covering two-thirds of the right thorax.

The amount of sanguineous fluid aspirated by thoracentesis, increased from 80 c.c. just prior to SK to 800 c.c. within 24 hours after SK. Four lytic treatments were administered of 200,000 units of SK over a 3-week period. There was complete evacuation of the loculated coagulum with expansion of the lung. The hemothorax was infected with *Bacterium coli*. SK treatments were supplemented by Chloromycetin intrapleurally and systemically. The area was sterilized in 3 weeks. There was complete clearing of the diseased area during the subsequent 3 months. The case was complicated by paraplegia and decubitus ulcers secondary to traumatic section of cord.

Patient T. S., white man, 33 years of age, with hemothorax of lower third of left chest which developed following vagotomy performed for peptic ulcer. He became available for SK therapy on the nineteenth postoperative day.

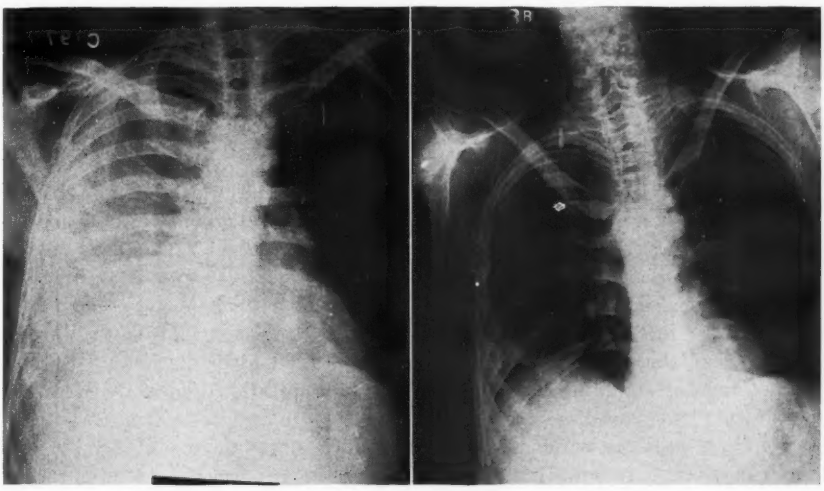


Fig. 9.—Case B. L. Infected hemothorax following bullet wound. *A*, Appearance on thirty-third day following injury and just prior to streptokinase therapy. *B*, Appearance one month later after four streptokinase treatments.

The amount of sanguineous fluid aspirated by thoracentesis increased from 44 c.c. just prior to SK to 325 c.c. within 24 hours after SK. Four lytic treatments were administered of 200,000 units of SK each over 10 days. There was extensive removal of the coagulum. Hemothorax was infected with hemolytic *Staphylococcus aureus*. The organisms persisted in spite of SK and penicillin therapy. The infection cleared following drainage through thoracotomy. During the ensuing 2 to 3 months, there was complete resolution of the diseased area.

It appears justifiable to conclude that in the 2 patients just described, an intractable situation due to clotted infected blood was rapidly and favorably altered following the action of SK which was supplemented by antimicrobial therapy and thoracotomy.

DISCUSSION

The observations on patients described in this report indicate that the intrapleural introduction of streptokinase (occurring in combination with streptodornase) is attended by extensive enzymatic fibrinolysis and liquefaction of hemorrhagic coagulums. In accordance with the details of the methods

described, the clinical results have been accomplished, without undue difficulties either immediate or late, and the action of the enzymes has favorably altered the course of many of the patients.

It should be recognized that as a therapeutic reagent, streptokinase acts solely as a means of effecting fibrinolysis and, in many cases, serves only as an adjunct to the broad management of hemothorax that may involve essential physiological and anatomical principles inherent in intrathoracic problems.

Further studies on the use of streptokinase are required in order to extend its clinical usages, to define more clearly the best methods of application, and to determine the degree to which its action may obviate or simplify other more difficult procedures.

SUMMARY

1. In 10 patients with massive sterile postpneumonectomy hemothorax, the injection of solutions of streptokinase-streptodornase was uniformly effective in liquefying rapidly the intrathoracic coagulum and affording its removal by aspiration.

2. Four patients with infection contained within the postpneumonectomy hemothorax were treated successfully in a similar manner, appropriately supplemented by the use of antibiotic reagents.

3. Eleven patients with traumatic hemothorax (bullet wound, stab wound, fractured ribs, and postoperative) with lungs in situ, have been treated by injections of the enzymes, often introduced simultaneously into multiple sites.

In 9 of the patients fibrinolysis was followed by a marked increase in the amount of sanguineous fluid removed by aspiration and extensive clearing of the pleural area.

4. In 2 patients with infected traumatic hemothorax an intractable state was rapidly and favorably altered by the use of streptokinase-streptodornase and was followed by recovery.

5. Details of the mechanism of the action of the streptococcal fibrinolytic principle have been reviewed and the practical aspects of its use have been described in detail.

The authors are indebted to Mr. John P. Goeller for the excellence of the photographs reproduced in this article, as well as for many other macro- and microphotographs he has supplied.

REFERENCES

1. Tillett, W. S., and Sherry, S.: The Effect in Patients of Streptococcal Fibrinolysin (Streptokinase) and Streptococcal Desoxyribonuclease on Fibrinous, Purulent, and Sanguineous Pleural Exudations, J. Clin. Investigation **28:** 173, 1949.
2. Christensen, L. R.: Methods for Measuring the Activity of Components of the Streptococcal Fibrinolytic System, and Streptococcal Desoxyribonuclease, J. Clin. Investigation **28:** 163, 1949.
3. Sherry, S., Tillett, W. S., and Christensen, L. R.: Presence and Significance of Desoxyribose Nucleoprotein in the Purulent Pleural Exudates of Patients, Proc. Soc. Exper. Biol. & Med. **68:** 179, 1948.
4. Tillett, W. S., Sherry, S., and Christensen, L. R.: Streptococcal Desoxyribonuclease: Significance in Lysis of Purulent Exudates and Production by Strains of Hemolytic Streptococci, Proc. Soc. Exper. Biol. & Med. **68:** 184, 1948.
5. Sherry, S., Johnson, A., and Tillett, W. S.: The Action of Streptococcal Desoxyribose Nuclease (Streptodornase), In Vitro, and on Purulent Pleural Exudations of Patients, J. Clin. Investigation **28:** 1094, 1949.

6. Tillett, W. S., Sherry, S., Christensen, L. R., Johnson, A. J., and Hazlehurst, G.: Streptococcal Enzymatic Débridement, Ann. Surg. **131**: 12, 1950.
7. Tillett, W. S., Sherry, S., Christensen, L. R., Johnson, A., and Hazlehurst, G.: The Effect in Patients of Streptococcal Fibrinolysin (Streptokinase) and Streptococcal Desoxyribose Nuclease (Streptodornase), Tr. A. Am. Physicians **62**: 93, 1949.
8. Tillett, W. S.: Studies on the Enzymatic Lysis of Fibrin and Inflammatory Exudates by Products of Hemolytic Streptococci. Harvey Lecture Series 1949-1950, Charles C Thomas, Publishers, Springfield, Ill. In press.
9. Tillett, W. S., Sherry, S., and Read, C. T.: To be published.
10. Read, C. T., and Berry, F. B.: The Utilization of Streptokinase-Streptodornase: In a Patient With Hemopneumothorax and a Patient With Postpneumonectomy Sanguineous Coagulum, J. THORACIC SURG. **20**: 384, 1950.
11. Christensen, L. R.: Protamine Purification of Streptokinase and Effect of pH and Temperature on Reversible Inactivation, J. Gen. Physiol. **30**: 465, 1947.
12. Guest, M. M., Daly, B. M., Ware, A. G., and Seegars, W. H.: A Study of Antifibrinolysin Activity in the Plasmas of Various Animal Species, J. Clin. Investigation **27**: 785, 1948.
13. Tillett, W. S.: The Occurrence of Antifibrinolytic Properties in the Blood of Patients With Acute Hemolytic Streptococcus Infections, J. Clin. Investigation **14**: 276, 1935.
14. Tillett, W. S., and Garner, R. L.: The Fibrinolytic Activity of Hemolytic Streptococci, J. Exper. Med. **58**: 485, 1933.
15. Milstone, H.: A Factor in Normal Human Blood Which Participates in Streptococcal Fibrinolysis, J. Immunol. **42**: 109, 1941.
16. Christensen, L. R., and MacLeod, C. M.: A Proteolytic Enzyme of Serum: Characterization, Activation, and Reaction with Inhibitors, J. Gen. Physiol. **28**: 559, 1945.
17. Loomis, E. C., George, C., Jr., and Ryder, A.: Fibrinolysin; Nomenclature, Unit, Assay, Preparation, and Properties, Arch. Biochem. **12**: 1, 1947.
18. Sellors, T. H.: Hemothorax, Lancet **248**: 143, 1945.
19. Melick, D. W., and Spooner, M.: Experimental Hemothorax, J. THORACIC SURG. **14**: 461, 1945.

PULMONARY PARAFFINOMA (LIPOID PNEUMONIA)

A Critical Study

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St. Louis, Mo.

THE wide spectrum of pulmonary infiltrates so long a problem to both radiologist and clinician is gradually being banded off and focused into recognizable segments.

Pulmonary paraffinoma, which is advanced lipoid pneumonia due to mineral oil, still continues to masquerade and elude diagnosis. We wish to emphasize that pulmonary paraffinoma can mimic lung cancer clinically, radiographically, grossly at the operating table, and is even mistakenly called cancer on frozen section. This mistake has been made by us and reported by others.

Laughlin's[1] report in 1925 on lipoid pneumonia in four infants and one adult was the first description of the disease in man and stimulated great interest. Pinkerton two years later reported six cases of lipoid pneumonia and for the first time presented a clear account of the pathologic events occurring after mineral oil reaches the pulmonary alveolus.

Ikeda,[2] in 1937, made the observation that lipoid pneumonia seen in infants differs pathologically from the usual lesion in the adult. Recognizing the tumorlike character of the advanced adult type lesion, he gave it the descriptive title paraffinoma.

Despite these early clear-cut descriptions, there has been a tendency in both the literature and practice toward a confusion of terms and meanings concerning lipoid pneumonia. The present study comprising a critical analysis of our own cases and an extensive review of the literature represents an effort on our part to define a clinical and radiographic picture which can be fairly consistently recognized. We have been fortunate in having the help of Pinkerton in this study, and he has personally reviewed all the sections in our own series.

The infantile type of lipoid pneumonia which is due to a variety of lipids is not as frequently seen by the thoracic surgeon as is the adult type. Goodwin's[3] excellent summary of the clinical picture of this disease stressed that the baby is either one suffering from a neurologic lesion resulting in loss of consciousness, absent cough reflex, or requiring tube feedings, or is debilitated and has been given oil medication. The child coughs, has rapid respirations, and fails to gain weight. Radiographically, infantile lipoid pneumonia exhibits infiltration in aspiration areas which persist unchanged for months. Lack of hilar adenopathy is a major point in differentiating the lesion from tuberculosis. The usual accentuation of bronchial markings seen in chronic inflammatory lesions is strikingly absent; there is little pleural reaction.

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The infantile type of lipoid pneumonia due to mineral oil represents temporally the initial stage of the adult type and consists of a process in which alveoli are occupied by oil-filled macrophages and free oil globules. The lesion is usually more extensive than the adult type and unaccompanied by the late changes of fibrosis and granuloma formation.

The adult type of lesion, with which we are chiefly concerned, usually occurs in older individuals who are habitual users of mineral oil orally, intranasally, or intratracheally. Neurogenic and mechanical interference to swallowing may be a factor, but is by no means always present. Mineral oil as such or in one of its medicated forms is the sole etiological agent. There may be no pulmonary symptoms or there may be such symptoms as chronic cough with or without sputum, hemoptyses, low-grade fever, frequent lower respiratory infections, and dyspnea on exertion. When compared with the minimal symptoms presented by the patient, the gross roentgenologic findings are usually strikingly greater than would be anticipated. Clinically and radiographically, the lesion is most often interpreted as a primary or metastatic tumor, or an unresolved pneumonia.

Radiographically, a pulmonary paraffinoma appears as a rather homogeneous shadow with sharply defined peripheral limits and a contrasting feathering of density at its hilar aspect; this latter point we feel is a particularly valuable diagnostic sign. This correlates well with the pathogenesis of the lesion, namely, the macrophage transport of the oil to the hilar lymph nodes along the peribronchial lymphatics. The lesion is located in recognized aspiration sites in greatest frequency, for example, lower lobes, apical divisions of lower lobes, and subapical segments of upper lobes. In other words, the lesion is segmental in location. Hilar adenopathy as seen in advanced carcinomas has never been recorded or observed by us. The shadows are permanent and incapable of significant resolution. The lesions are often multiple and are often bilateral. The resemblance to the shadows cast by tumors is marked.

For an understanding of the pathologic picture of the lesions of lipoid pneumonia we are indebted chiefly to Pinkerton[4] and the following description is drawn in part from his studies. First of all, the pulmonary pathology varies with the type of oil and the length of time it has been in the lung. This explains the difference between the infantile and adult types. Pathologically, pulmonary paraffinoma represents a late stage of granulomatous productive inflammation, often clearly localized, densely fibrous and neoplastic in appearance. Mineral oil is inert and acts purely as a foreign body in pulmonary tissues. Elimination from the lung occurs by two methods: (1) expectoration and (2) transport to regional lymphatics in phagocytic cells.

Early, the adult type of lipoid pneumonia grossly resembles the gray hepatization stage of lobar pneumonia. The older adult type lesion or paraffinoma consists of one or a group of nodular masses of varying size lying in close proximity to major bronchial trunks. The mass is sharply demarcated from adjacent lung parenchyma in its periphery. The overlying pleura may be thickened and puckered. The mass is firm, and the cut surface is mottled yellow to grayish-yellow. Small cavities filled with oil are seen and the entire cut surface is oily. Its center is made up of a lobar or lobular bronchus.

A lesion is acceptable as a paraffinoma when the histologic picture described is found and the presence of mineral oil is demonstrated by positive staining with Sudan red and absence of staining with osmic acid. The failure of mineral oil to stain with osmic acid was first pointed out by Pinkerton.[4] Extraction of oil chemically, saponification tests, iodine numbers, and fluorescence tests are not necessary for establishing the diagnosis.[5]

In 1943, Wood[6] reported a case of bilateral alveolar cell carcinoma of the lung associated with lipoid pneumonia due to mineral oil. He attempted to establish an etiological relationship between lipoid pneumonia and the development of carcinoma. He quoted Twort and Lyth[7] who had found that several fractions of natural mineral oil produced primary lung tumors in mice. Wood compared his case with Jagziekte of sheep. One of our cases of pulmonary paraffinoma, or adult type lipoid pneumonia, exhibited epithelial proliferations of such a degree that a frozen section diagnosis of cancer of the lung was made. This epithelial proliferation was noted in the experiments of Pinkerton.[4] Sante[8] reported two cases of squamous carcinoma of the lung occurring with lipoid pneumonia. The carcinoma arose within the lesion in one of the two cases. Microscopic sections were interpreted as showing carcinoma plus lipoid pneumonia. The regional nodes contained no cancer.

Eleven authors[2, 8-14] writing from 1933 until December, 1949, have reported adult type lesions which were tumorlike in their clinical aspects. Janes[14] of this association reported two cases in October, 1947.

CASE REPORTS

CASE 1 (B. A.).—This 61-year-old white woman entered Barnes Hospital on Dec. 19, 1946, with a history of two months' duration of malaise, chills, fever, and right anterior chest pain associated with cough, and a twelve pound weight loss. The referring doctor made a diagnosis of virus pneumonia. The patient had used oral mineral oil on retiring three times a week for many years. She had suffered from cardiospasm for thirteen years. Physical examination revealed a poorly-nourished, chronically ill-appearing, white woman without clubbing of the fingers. Her temperature on entry was 39.4° C. Dullness to percussion and decreased breath sounds were noted over the region of the right upper lobe posteriorly. Bronchoscopy revealed nothing other than reddening and swelling of the mucous membrane of the right upper lobe orifice. Esophagoscopy revealed spasm of the cardia and no other abnormalities. A clinical diagnosis of carcinoma or virus pneumonia was made. X-ray examination of the chest revealed two somewhat spherical areas of increased density, one in the subapical segment of the right upper lobe and one in the apical segment of the right lower lobe. At thoracotomy a firm mass in the subapical segment of the right upper lobe and another smaller lesion in the superior division of the right lower lobe were encountered. The cut surface of the lesion was yellowish-gray in color. There was destruction of the architecture. Yellowish conglomerate areas, 3 to 4 mm. in diameter, containing oil cysts were present. In some areas the pleura had thickened to 3 to 4 mm. Microscopic examination of the lesion revealed a typical paraffinoma in which the lipid stained with scarlet red and did not stain with osmic acid.

CASE 2 (E. L.).—This 46-year-old white man entered Barnes Hospital on May 4, 1947, with the chief complaint of chest pain on the left and fatigability for three years. An x-ray examination before admission had revealed a left lower lobe shadow. Bronchograms performed two weeks before the patient's hospitalization revealed some bronchiectasis in the left lower lobe. The patient gave a history of a tracheal intubation at the age of 6 years and

Fig. 1.—Roentgenogram of C. M., Case 3, showing obvious cystic changes in the upper lobes and the paraffinoma in the right lower lobe with relatively sharp periphery and feathering of the hilar aspect of the density.

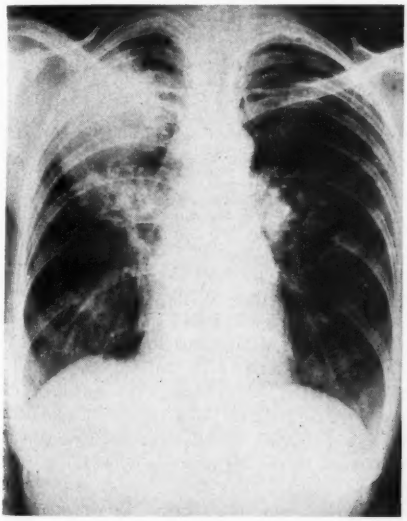

Fig. 2.

Fig. 3.

Figs. 2 and 3.—Posteroanterior and right lateral roentgenograms of B. A., Case 1, demonstrate lesions in two aspiration sites: the subapical segment of the right upper lobe and and the apical segment of the right lower lobe.

hoarseness which had persisted from that time. He had suffered from chronic sinusitis and had been treated by an oily nasal spray and nose drops for an undetermined length of time. There was no history of hemoptysis. Physical examination revealed a thin white man without findings referrable to the chest and no clubbing of the fingers. Bronchoscopy was negative. At left thoracotomy a 4 by 3 cm. mass was present in the posterior basal segment of the left lower lobe. The overlying pleura was thickened and at the base and over the lateral pleura, tumorlike 3 to 5 mm. in diameter yellowish lesions were seen. On cut surface, a yellowish gray-black mottled surface was encountered which oozed a colorless oil. Microscopic examination of the lesion revealed a typical paraffinoma which stained with Sudan III and did not stain with osmic acid.

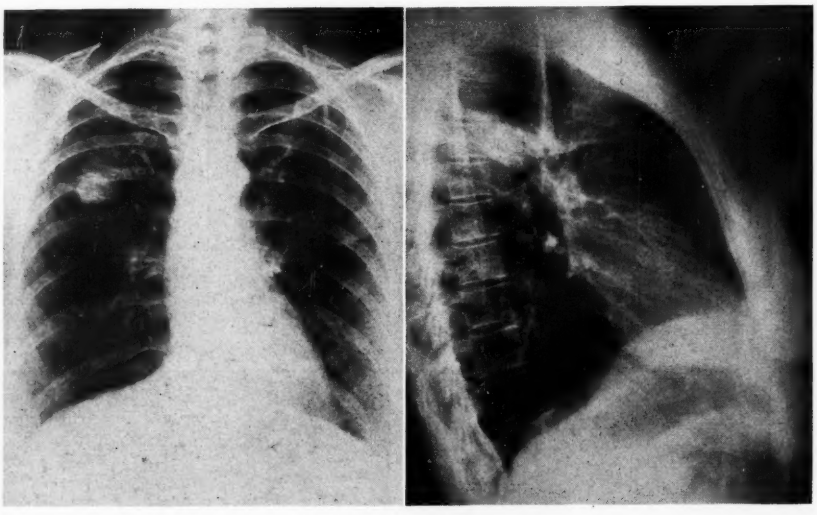

Fig. 4. Fig. 5.

Figs. 4 and 5.—Posterior-anterior and right lateral roentgenogram of R. B., Case 4, which illustrate the peripherally well-circumscribed lesion in the subapical segment of the right upper lobe.

CASE 3 (C. M.).—This 51-year-old white man entered Barnes Hospital on Aug. 13, 1947, complaining of dyspnea of one year's duration, productive cough of six months' duration, and frequent lower respiratory infections for many years. He had had no hemoptyses. A bronchogram done two weeks before entry by the referring doctor was essentially noncontributory. The patient had used mineral oil at night for a laxative for as long as he could remember. Physical examination revealed a well-developed white man with an area of decreased resonance to percussion posteriorly over the right lower lobe region. There was no clubbing of the fingers. Roentgenologic findings consisted of bilateral emphysematous bullae in the upper lobes and a large radiopaque area in the right lower lobe which was thought to be a carcinoma. Bronchoscopic findings consisted of diffuse infiltration in the right main-stem bronchus with large amounts of thick, tenacious sputum being produced on that side. At operation the lesion was thought to be a carcinoma and a right pneumonectomy was performed. There were huge cysts in the right upper lobe and the posterior basal segment of the right lower lobe was occupied by a firm, 5½ by 4 by 4 cm. mass, peribronchial in location, with ill-defined margins and a yellowish-gray mottled oily cut surface. Microscopic examination revealed a typical paraffinoma which stained with Sudan III and not with osmic acid. The regional lymph nodes contained macrophages filled with mineral oil.

CASE 4 (R. B.).—This 52-year-old white woman entered Barnes Hospital in July, 1948, because a shadow was found in the right lung field on routine fluoroscopy. The patient had suffered from cardiospasm for ten years. She had used mineral oil at night for constipation for three to four years and had used Vick's VapoRub in the nostrils for colds and chronic sinusitis. She had no pulmonary symptoms and had had no hemoptysis. Physical examination revealed a well-developed, moderately obese white woman. Examination of the chest was negative. There was no clubbing of the fingers. X-ray examination revealed a circumscribed area of increased density in the right upper lobe in the subapical segment. Bronchoscopy was nonrevealing. A clinical diagnosis of lipoid pneumonia was made with the presence of carcinoma being strongly considered. At right thoracotomy the lesion was found to be a

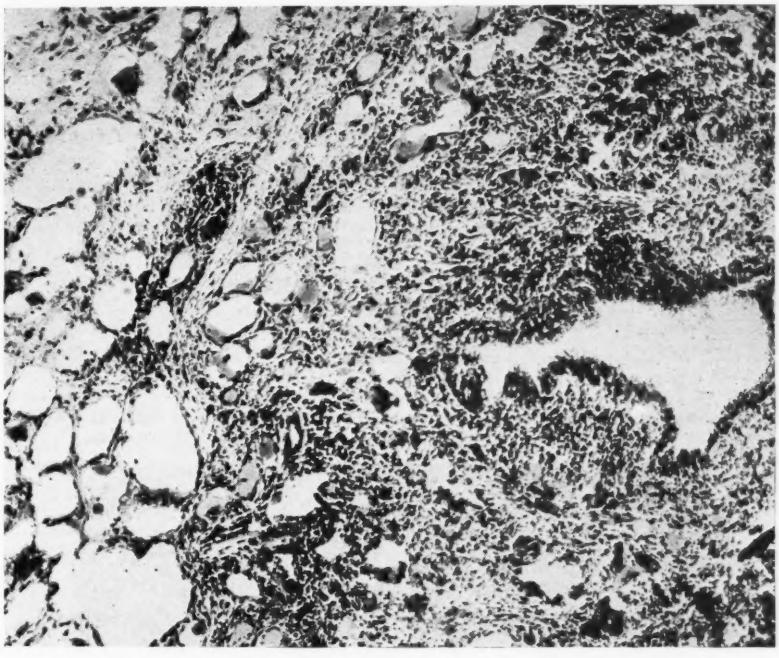

Fig. 6.—This photomicrograph of a hematoxylin and eosin section of the paraffinoma in Case 4, well demonstrates the variable sized spaces which contained oil.

5 cm. spherical mass in the subapical segment of the right upper lobe. Frozen section was done and was said to reveal carcinoma. A right pneumonectomy was performed. Satellite nodules were seen in the lower lobe. On cut surface the lesion was seen to be yellowish-gray, mottled, and exhibited sharp areas of transition between normal and involved parenchyma. There were small cystic spaces full of oil. Microscopic examination of the lesion revealed a typical paraffinoma with failure of the lipid to stain with osmic acid.

CASE 5 (E. H.).—This 62-year-old white man entered Barnes Hospital in October, 1948. He was asymptomatic and gave a history of a lung lesion being found on a chance x-ray examination by a mobile unit. Bronchograms had been made by the referring physician and revealed an obstruction to the right middle lobe. He gave a history of using oily nose drops for chronic sinusitis for a period of about three years which ended five years before entry. He was a well-developed, well-nourished, white man with an anterolateral wedge-shaped area of dullness and decreased breath sounds over the right hemithorax. There was

no clubbing of the fingers. A clinical diagnosis of carcinoma of the lung was made although repeated sputa were negative for tumor cells. Roentgenologic findings are shown in the accompanying photographs. On bronchoscopy the only abnormality in the tracheobronchial tree was posterior displacement of the orifice of the right lower lobe bronchus so that the

Fig. 7. Fig. 8.

Figs. 7 and 8.—Posterior-anterior and right lateral roentgenogram of E. H., Case 5, showing middle and right lower lobe shadows which led to a thoracotomy.

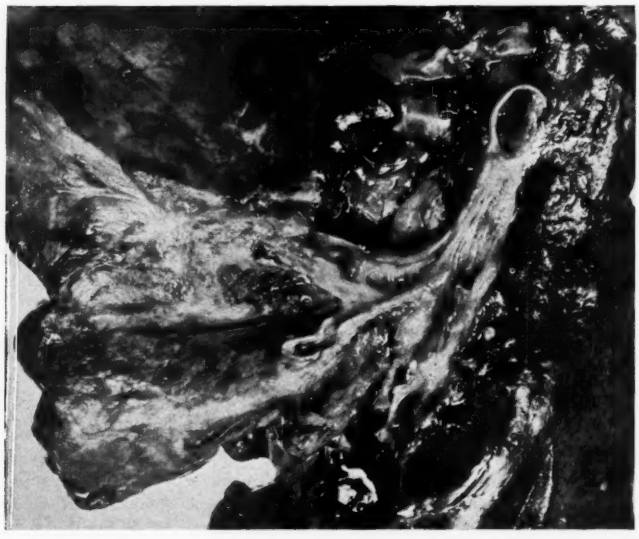

Fig. 9.—This photograph exhibits a cross section of the middle lobe lesion in which the gross resemblance to carcinoma is marked.

right middle lobe orifice was in line with the right main-stem bronchus. A right thoracotomy was performed and a yellowish-gray firm mass involving the parenchyma of the superior portion of the middle lobe causing extensive puckering of the pleura was found. This was associated with yellow-gray implants over the visceral and parietal pleurae and the pericardium. The lesion was thought to be a carcinoma with metastases to the pericardium and both pleural surfaces. A frozen section of the lesion was obtained and interpreted as showing carcinoma. A palliative resection was decided upon and carried out. Sections of the lesion described revealed a fibrotic lesion with complete erasure of the normal pulmonary architecture in which microscopic oil-filled spaces separated by fibrous tissue were seen. In some areas macrophages containing oil droplets could be seen. There were focal collections of lymphocytes. The regional lymph nodes contained macrophages with oil globules in their cytoplasm. The pulmonary lesion was a typical paraffinoma. The lipid material in the oil-filled spaces stained with Sudan III and failed to stain with osmic acid.

CASE 6 (R. O.).—This 52-year-old white man entered Barnes Hospital on April 7, 1949, because his physician discovered a lesion in the left lower lobe during a routine fluoroscopy. The patient had suffered for years from chronic sinusitis and constipation and had used mineral oil preparations for both lesions. He denied all pulmonary symptoms. He had never suffered an hemoptysis. Physical examination revealed a fairly well-developed white man who exhibited no physical findings of note on examining the chest. There was no clubbing of the fingers. Bronchoscopy was not performed. A clinical diagnosis of possible carcinoma in the left lower lobe was made preoperatively. At left thoracotomy the lesion was thought to be a paraffinoma on the basis of gross findings of a 5 by 5 cm. hard, mottled, yellow lesion in the anterior basal portion of the left lower lobe. Cut surface revealed miliary oil-filled spaces. Microscopic section of the lesion revealed a typical paraffinoma.

SUMMARY

1. Pulmonary paraffinoma is not uncommonly encountered by the thoracic surgeon. The lesion is clinically, radiographically, at operation, and even at frozen section confused with carcinoma, either primary or metastatic. Many lobes have been needlessly sacrificed by failure to recognize the true nature of this lesion.

2. Clinically the patient is usually an adult who may have no symptoms or symptoms mimicking bronchiogenic carcinoma, even hemoptysis. The patient almost always gives a history of use of mineral oil or one of its medicated preparations either orally, nasally, or even intratracheally. There may or may not be an associated neurologic lesion resulting in impairment of ability to swallow or mechanical interference with deglutition as with diverticula and cardiospasm.

3. Roentgenologically, circumscribed tumorlike shadows in aspiration areas without hilar adenopathy and with peribronchial infiltration, especially in the lower lobes, are present. The lesion is roentgenologically more striking than the patient's clinical symptoms would lead one to expect. The lesions are often multiple and frequently bilateral.

4. At operation the lesion may so mimic carcinoma as to result in needless pneumonectomy when lobectomy would have sufficed.

5. Pulmonary paraffinoma is often misdiagnosed and it is hoped that renewed attention to the subject will stimulate more accurate diagnoses. There has been some evidence suggesting that mineral oils are carcinogenic.

REFERENCES

1. Laughlin, G. F.: Studies on Pneumonia Following Nasopharyngeal Injections of Oil, Am. J. Path. **1:** 407-414, 1925.
2. Ikeda, K.: Lipoid Pneumonia of Adult Type (Paraffinoma of Lung): Report of Five Cases, Arch. Path. **23:** 470-492, 1937.
3. Goodwin, T. C.: Lipoid Cell Pneumonia, Am. J. Dis. Child. **48:** 309-326, 1934.
4. Pinkerton, Henry: Oils and Fats: Their Entrance Into and Fate in Lungs of Infants and Children: Clinical and Pathological Report, Am. J. Dis. Child. **33:** 259, 1927.
5. Wolman, Irving J., and Bayard, Anna B.: Experimental Aspiration Pneumonia; Fluorescence and Pathology, Am. J. M. Sc. **202:** 542-553, 1941.
6. Wood, E. H., Jr.: Unusual Case of Carcinoma of Both Lungs Associated With Lipoid Pneumonia, Radiology **40:** 193-195, 1943.
7. Twort, J. M., and Lyth, R.: The Concentration of Carcinogenic Materials in Mineral Oils by Distillation Processes, J. Hyg. **39:** 161-169, 1939.
8. Sante, L. R.: The Fate of Oil Particles in the Lung and Their Possible Relationship to the Development of Bronchiogenic Carcinoma, Am. J. Roentgenol. **62:** no. 6, December, 1949.
9. Stokes, Arthur M.: Lipoid Pneumonia, Am. Rev. Tuberc. **47:** 348-350, 1943.
10. Houck, G. H.: In Medical Papers Dedicated to Henry Asbury Christian, Baltimore, 1936, Waverly Press, Inc., p. 463.
11. Brown, A. L., and Biskind, G. R.: Differential Diagnosis Between Lipoid Pneumonia and Pulmonary Neoplasm: Report of Cases Treated by Partial Lobectomy, J. A. M. A. **117:** 4-6, 1941.
12. Thomas, H. M., and Rienhoff, W. F.: Lipoid Cell Pneumonia: Adult Type, South. M. J. **32:** 1077-1080, 1939.
13. Fischer-Wasels, B.: Tödliche Lungenschrumpsfung durch Gebrauch von Mentholöl, Frankfurt. Ztschr. f. Path. **44:** 412, 1933.
14. Janes, R. M.: Pneumonia (From Using Oil Drops) Simulating Bronchiogenic Carcinoma, J. THORACIC SURG. **16:** 451-457, 1947.

DISCUSSION

DR. J. E. DAILEY, Houston.—We have had three cases of lipoid pneumonia upon which we have operated, two of which closely resembled the appearance so well described by Dr. Berg. I would like to show one case that was rather different, which began as an acute inflammatory type of lesion. This was a man about 38 years old who had been in the habit of using oily nose drops for several months.

(Slides.) This started with an acute onset of fever, 101° to 102° F., and the x-ray appearance of pneumonia, which apparently did not resolve. The first slide, in March, 1949, is shown on the left; on the right, one week later, showing a marked change in the appearance of the lesion which at first looked like an inflammatory type lesion. He improved somewhat and his temperature decreased. However, he began to expectorate some bloody sputum. (Slide.) This shows, two months after the first roentgenograms were taken, an atelectatic type of lesion. This was the time at which we first saw the patient and, of course, without the first two roentgenograms our first impression would be carcinoma of the lung. When we obtained the first roentgenograms there was a little doubt because of the inflammatory appearance. Bronchoscopic studies were performed, Papanicolaou slides and Gelfoam sponge preparations were made. All were negative for any evidence of malignant cells.

We operated on him and the following is a postoperative roentgenogram. At operation the lesion still appeared to be an inflammatory lesion, rather than tumor, so we elected to do only an upper right lobectomy. The next slide shows the granulomatous type of lesion that was present in the apical division. The next slide shows the microscopic specimen, illustrating well the lipoid content of the cells.

DR. JOHN J. HARTER, Louisville, Ky.—The industrial occurrence of paraffinoma of the lung has been mentioned before in the literature. I simply want to bring it to your attention again. We have had two patients in whom the history was very definite; one was a Diesel motor mechanic who inhaled Diesel fuel oil. The other was a gear-cutter operator. Gear-cutter machines, I am told, use oil under very high pressure; the lines occasionally break and he would inhale the oil. I think it is well to remember that the increasing use of

oil under high pressure may well give us more of these paraffinomas in the future. Both our patients were operated upon for lung abscess and lobectomies were done. The paraffinoma was found to be the cause of the lung abscess in each case.

DR. JOHN R. MC DONALD, Rochester, Minn.—I wish to point out that not all oil granulomas of the lung are due to mineral oil. I want to mention three cases which illustrate the various types of oil granuloma of the lung which are of importance to the surgeon.

The first case is that of a young man, 17 years of age, who had a history of chills and fever of four months' duration. A roentgenogram of his thorax disclosed a shadow in the left lower pulmonary field. A left lower lobectomy was done. An aberrant vessel to this left lower lobe was found coming from the aorta. After careful dissection of the bronchial tree of the lower lobe, it was determined that there was no communication between this bronchus and the rest of the bronchial tree. The lobe itself was airless, consolidated, and yellow. The diagnosis was pulmonary sequestration with lipoid pneumonitis of the lobe. Microscopically the pulmonary alveoli and bronchi were filled with inflammatory cells and a great deal of lipid was present in phagocytes. Gross chemical studies of this tissue revealed a total lipoid content of 4.1 per cent made up of cholesterol esters, lecithin, and fatty acids. In this case it is obvious that the oil is the result of a breakdown of the cells in the lobe by which process invisible lipids become visible.

The second case is that of a young woman who had bronchiectasis. In order to determine the extent of the bronchiectasis, a bronchogram had been made with the use of Iodochloral. The oil base for Iodochloral is peanut oil. At the time of lobectomy, two weeks after the bronchogram had been made, consolidated pinkish-yellow areas were found in the resected lobe which microscopically demonstrated an oil granuloma. Gross chemical studies were done on the consolidated granulomatous areas and the nonconsolidated areas of the same lobe. These demonstrated a large amount of iodine in the consolidated granulomatous areas and practically none in the nonconsolidated areas. Such evidence is proof that this granuloma was due to the Iodochloral.

The third case is that of a patient having a mineral oil granuloma. Thoracotomy had been done to determine the nature of a roentgenographic shadow in the lung. At the operating table a piece of tissue was removed from the mass for microscopic diagnosis and a tentative diagnosis of mineral oil granuloma was made from the fresh frozen section. Lobectomy was then done. The oil was extracted from the lesion with fat solvents. It proved nonreactive to acids and alkalies. It was, therefore, concluded that this oil belonged to the petroleum group of lipids. After operation, a history of repeated instillations of mineral oil was obtained in regard to this patient.

I consider it much more accurate to determine the type of oil present in these various granulomas by means of gross chemical studies than by the use of histologic preparations utilizing the various fat stains.

DR. A. J. GRACE, London, Ontario.—I want to emphasize what was brought out by Dr. Berg and Dr. Burford—that this is a problem which we can diagnose wrongly unless alive to its existence and frequency. I made a mistake, too, and want to present briefly slides which illustrate one such case where pneumonectomy was done. I think the principle must be stressed, during these days when we are urging general surveys of chest cases and correct treatment for any circumscribed or other mass that is found, that we must not overtreat these cases nor do unnecessary major operations, and this case is certainly an unfortunate illustration of that point.

(Slides.) This is a man nearly 60 years of age, who had minimal symptoms. You will note at the right base a collapsed middle lobe. The picture does not show well a circumscribed mass which was picked up in the course of x-ray studies. The next slides show the specimen removed by pneumonectomy. The process involved the lower as well as the middle lobe, and that was the reason for the pneumonectomy.

The principle to be emphasized is that which Dr. Berg brought out, that we must be on the lookout for this lesion. It is a relatively common one. Mineral oil is being used too much by the public, it has some dangers, and I think we should make that fact known. This case illustrates the point that the symptoms, although marked, were not in keeping with the suspected diagnosis of carcinoma, and I think we should have considered that. We have seen one similar case since in which operation was avoided.

DR. BURFORD (closing).—Dr. Berg has indicated the reason for our interest in this lesion. Failure to recognize the probability of a paraffinoma by neglecting to elicit the pertinent historical facts, and lack of proper conception of the radiographic appearance, will often lead to the development of a cycle of vicious events which may even encompass the surgical pathologist. The result is the needless sacrifice of normal lung. Recognition of the principles stressed by Dr. Berg has enabled us to diagnose this disease with fair accuracy, and leads us to believe that far fewer mistakes will be made in the future.

Dr. Grace has shown a beautiful example of a true paraffinoma. I would like to thank him for his remarks and particularly for his choice of a case.

Dr. McDonald's case was not what we are talking about today. We purposely and carefully excluded this type of lesion from our group in order that clarity of thinking may be attained in relation to the true paraffinoma.

We disagree vehemently that one needs more than the hematoxylin and eosin and osmic acid stains to diagnose histologically the true paraffinoma.

SURGICAL TREATMENT IN PULMONARY COCCIDIOIDOMYCOSIS

Preliminary Report of Thirty Cases

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SURGICAL management of thirty cases of pulmonary coccidioidomycosis is reviewed. Operative criteria are established. The results obtained in this limited number of selected cases are extremely encouraging and appear to warrant further analysis.

The complications of pulmonary coccidioidomycosis are: (1) fibrosis of varying degrees of parenchymal infiltration; (2) coccidioma (this term has been employed by the authors to represent the circumscribed density occurring in the lung parenchyma, as a coccidioidal granuloma, comparable to a tuberculoma and indistinguishable both roentgenologically and anatomically); (3) dissemination; (4) pleural effusion; (5) bronchiectasis (extensive study of bronchoscopy and bronchography findings has yielded considerable information which tends to prove that bronchiectasis is a common sequela of pulmonary coccidioidomycosis); and (6) cavitation.

Of these six complications, cavitation presents the greatest dilemma to the attending physician as to both prognosis and treatment. The course of cavities may be divided into an acute and a chronic phase. The acute cavity appears with the parenchymal infiltration and disappears completely with the resolution of the infiltration. The typical chronic cavity persists apparently with a minimal or no zone of fibrosis around it. The minimum period between these two phases is usually from six to eight weeks. Another interesting finding is the lack of correlation between the extent of parenchymal involvement during the acute phase and the development of complications.

The complications occurring in the medically treated or untreated cavities are:

1. Giant cavity
2. Secondarily infected cavities
3. Rupture of cavity
   a. spontaneous pneumothorax
   b. empyema
   c. bronchopleural fistula
4. Nonexpansile lung
5. Hemoptysis
   a. continued
   b. severe

AUTHORS' SERIES

Significant data pertaining to the thirty patients included in this series are summarized in Table I. Diagnosis was confirmed in all instances by one or

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TABLE 1

CASE NUMBER	AGE (YR.)	SEX	RACE	DURATION OF ILLNESS	MEDICAL TREATMENT EMPLOYED	DIAGNOSIS CONFIRMED BY	OPERATIVE INDICATIONS	OPERATIVE PROCEDURE	COMPLICATIONS	PRESENT CONDITION
1. C. S.	36	M	W	8 yr.	Rest cure; diagnosed tbc until 1945	Spherules in sputum; pos. blood	Giant cavity, secondarily infected	Left upper lobectomy	None	Symptom free; ret. to work 3rd P.O. wk.
2. J. L.	48	M	W	Unknown	Rest cure; rt. phrenic; penicillin IM and aero.	Spherules in sputum; pos. blood; high blood titer, bordering on dissemination	Giant cavity, secondarily infected	Right pneumonectomy	Cocc. empyema controlled by thoracoplasty	Symptom free; ret. to work 4th P.O. mo.
3. L. L.	49	M	Mexican	4 yr., 8 mo.	Rest cure; penicillin IM and aero., diagnosed as lung abscess	History pos. skin test; neg. tbc; typical thin-walled cavity	Giant cavity, secondarily infected	Right pneumonectomy	Died of coronary thrombosis 4th P.O. day	
4. F. D.	47	M	W	8 mo.	Rest cure	Spherules; pos. blood	Giant cavity, secondarily infected	Right pneumonectomy	None	Symptom free; ret. to work 2nd P.O. mo.
5. F. T.	29	M	W	9 yr.	Rest cure; bilat. phrenic; bilat. pneumothorax; pneumoperitoneum	Spherules; pos. blood; pos. tbc sputum	Giant cavity	Right pneumonectomy	None	Symptom free; released from San. 8 mo. P.O.
6. J. P.	23	M	W	6 yr.	Pleural effusion, aspiration; bed rest	Pos. skin; neg. tbc; typical history and x-ray	Hemoptysis; large cavity	Right lower lobectomy	None	Symptom free; ret. to work
7. J. T.	19	M	W	5 mo.	Partial bed rest	Spherules from pleural fluid; culture pos.; pos. serology, range of dissemination	Empyema	Left lung decortication with removal of cyst	None	Symptom free; ret. to work 3rd P.O. wk.
8. G. R.	43	M	W	3 yr.	Bed rest, intermittent	Spherules in pleural fluid; pos. blood and pos. skin	Empyema	Decortication, left lung	None	Symptom free; ret. to work 2nd P.O. mo.

9. G. J.	35	F	W	21 mo.	Intermittent bed rest	Spherules in sputum; pos. skin, neg. tbc; G.P. pos. for tbc	Hemoptysis; gen. malaise	Segmental lobectomy, left upper	None	Symptom free; ret. to work 2nd P.O. mo.
10. W. J.	33	F	W	9 mo.	Bed rest, intermittent	Pos. skin; pos. blood	Hemoptysis; gen. malaise	Segmental rt. upper lobe	None	Symptom free; ret. to work 3rd P.O. wk.
11. L. C.	30	F	W	9 mo.	Bed rest; rt. pneumothorax, pneumoperitoneum	Pos. skin; pos. blood; pos. sputum culture	Blocked ballooning cavity	Right lower lobectomy	None	Symptom free; ret. to work 3rd P.O. wk.
12. W. D.	54	M	W	2 yr.	None	Culture pos.; path. specimen, spherules	Differential of carcinoma and coccidioma	Segmental left lower lobe	None	Symptom free; ret. to work 4th P.O. wk.
13. J. M.	31	M	W	4 yr.	Bed rest 16 mo.; rt. pneumothorax; pneumoperitoneum; rt. phrenic, temporary	Pos. skin; pos. blood; pos. sputum; sputum pos. tbc	Failure of medical Rx; hemoptysis	Right lower lobectomy	Pleural effusion lt. tbc contra-lat. lung; actinomycosis, rt. lower lobe	Symptom free; ret. to work 3rd P.O. mo.
14. F. S.	15	M	W	12 mo.	Bed rest; phrenic crush; pneumothorax; pneumoperitoneum	Pos. skin; pos. blood; pos. sputum	Secondarily infected cavity	Segmental lobectomy	None	Symptom free; ret. to work 4th P.O. wk.
15. M. L.	36	M	W	6 mo.	Bed rest	Culture positive	Empyema, left pleural space	Decortication, empyema space	None	Symptom free; ret. to work 6th P.O. wk.
16. C. B.	47	M	W	2 yr.	Bed rest	Skin test pos.; comp. fix. neg.; typical history and thin-walled cavity	Cavitation, secondarily infected	Pneumonectomy	Associated primary ca. of the lung	Symptom free; ret. to work 2nd P.O. mo.
17. B. S.	17	F	W	20 mo.	Bed rest	Pos. skin; neg. tbc; typical history and typical thin-walled cavity	Hemoptysis, secondarily infected	Rt. upper lobectomy	None	Symptom free; ret. to work 3rd P.O. wk.

(Continued on following pages.)

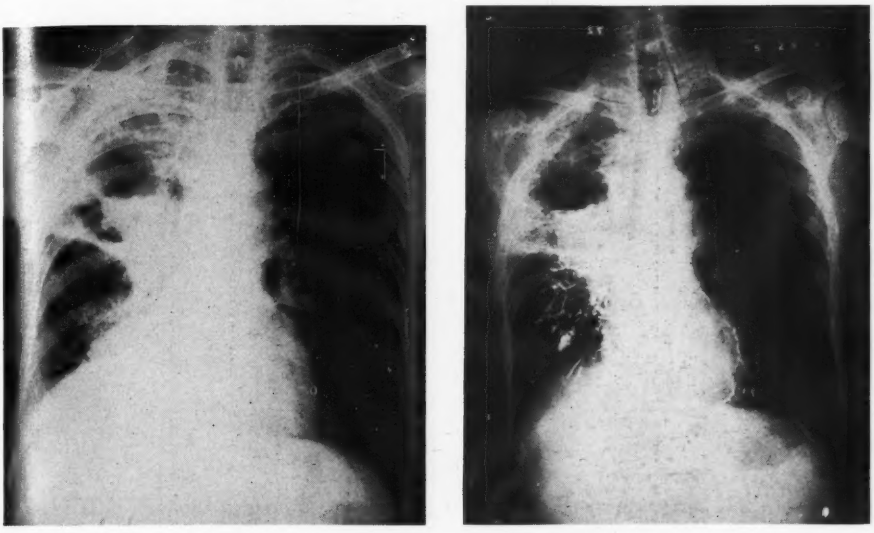
TABLE I—CONT'D

CASE NUMBER	AGE (YR.)	SEX	RACE	DURATION OF ILLNESS	MEDICAL TREATMENT EMPLOYED	DIAGNOSIS CONFIRMED BY	OPERATIVE INDICATIONS	OPERATIVE PROCEDURE	COMPLICATIONS	PRESENT CONDITION
18. R. L.	36	F	W	4 mo.	Bed rest; penicillin	Pos. skin test; pos. culture from specimen	Blocked secondarily infected cavity	Right lower lobectomy	None	Symptom free; ret. to work 2nd P.O. mo.
19. M. S.	40	F	W	22 mo.	Penicillin; bed rest	Pos. skin test; pos. blood	Hemoptysis, giant cavity, secondarily infected	Right lower lobectomy	None	Symptom free; ret. to work in 6 wk.
20. M. C.	38	M	W	Unknown	None	Spherules; pos. skin test; neg. tbc	Expanding density, rt. lower lung	Segmental resection	Prolonged pocket of fluid	Symptom free; ret. to work 3rd P.O. mo.
21. C. A.	39	M	W	Unknown	None	Spherules from specimen; pos. skin; neg. tbc	Rounded density rt. upper lobe; diff. bronchiogenic ca.	Segmental resection	None	Symptom free; ret. to work 3rd P.O. wk.
22. M. K.	36	F	W	16 mo.	Pneumothorax; bed rest	Pos. skin test; pos. comp. fix.	Continued hemoptysis	Left upper segmental lobectomy	None	Symptom free; ret. to work on 2nd P.O. wk.
23. R. S.	34	M	W	12 yr.	Bed rest; drainage of empyema, 2-9-40	Spherules in pleural fluid	Ruptured cavity mixed empyema; bronchopleural fistula; nonexpansile lung	Decortication supplementary thoracoplasty	None	Symptom free; ret. to work 4th wk. P.O.
24. E. J.	30	M	C	22 mo.	Bed rest; antibiotics	Pos. skin test; pos. blood; spherules in sputum	Hemoptysis, secondarily infected cavity	Left upper lobectomy	P.O. atelectasis controlled by bronchoscopy and aspiration	Symptom free; delayed P.O. re-expansion

25. V. R.	42	F	W	7 yr.	Antibiotics and sulfonamides	Pos. skin test; tbc neg.; typical thin-walled cavity	Bronchiectasis, secondarily infected	Rt. upper and middle lobectomy	None	Symptom free; ret. to work in 4 wk.
26. M. S.	26	M	C	9 mo.	Bed rest	Microscopic section of surgical specimen; comp. fix. neg.	Cavitation with severe and continued hemoptysis	Lt. upper lobectomy	None	Returned to work in 2 wk.
27. D. B.	41	M	W	Pleural effusion	Bed rest, thoracentesis	Neg. skin test; spherules recovered on culture; comp. fix. neg.	Cavity and unexpanded lung	Decortication, segmental resection of cavity	None	Returned to work in 8 wk.
28. L. H.	19	M	W	4 mo.	Bed rest, thoracentesis	Spherules found in spec. by microscopic examination; pos. skin test; tbc neg.; comp. fix. neg.	Pleural effusion; unexpanded lung; broncho-pleural fistula	Segmental lobectomy, dorsal div., lt. lower lobe and complete decortication	None	Complete reexpansion, returned to school
29. I. U.	45	F	W	1 yr.	Bed rest; pneumothorax; pneumonolysis	Pos. skin test; pos. tbc; acid-fast in sputum; confirmed by microscopic section, *Coccidioides immitus;* serology equivocal	Failure of collapse therapy	Rt. upper lobectomy		Returned to tbc sanatorium for further observation
30. L. C.	25	M	W	3 yr., 3 mo.	Observation for rounded density	Pathological section and culture; comp. fix. neg.; skin test pos.	Expanding lesion; cavity from shelling out of coccidioma	Rt. lower lobectomy	None	Returned to work in 4 wk.

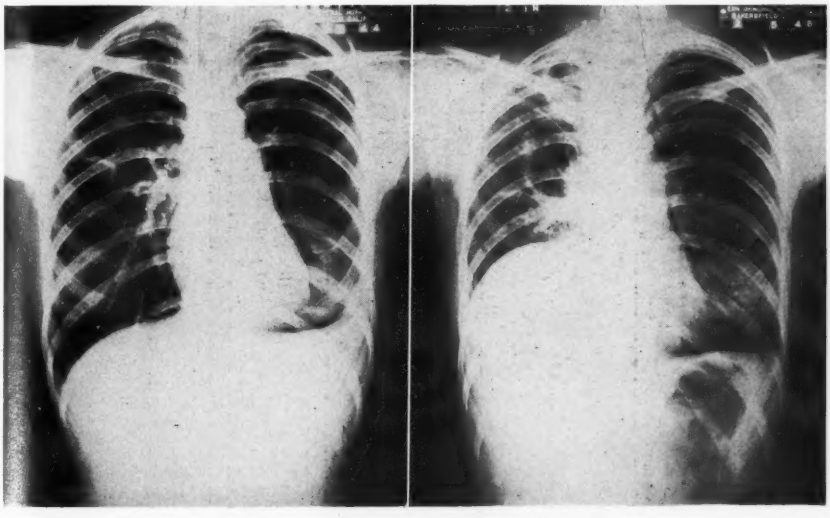
A. *B.* *C.*

Fig. 1 (Case 2).—*A*, Giant cavity; *B*, bronchiectasis, lower right lung field; *C*, postoperative.



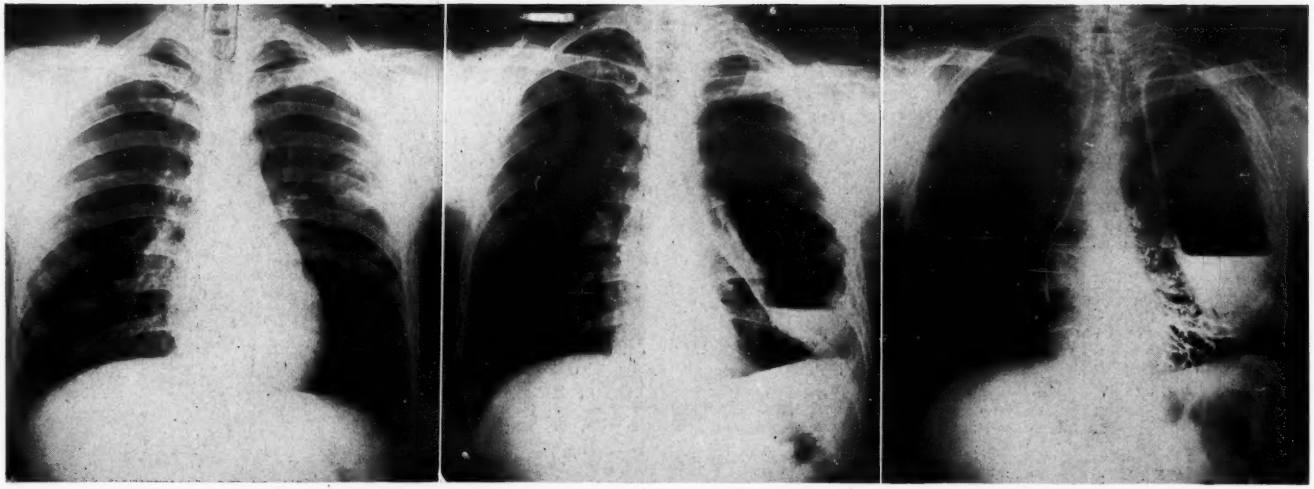
A. *B.*

Fig. 2 (Case 3).—*A*, Secondarily infected cavity with pyogenic organisms; *B*, bronchiectasis of right middle and lower lobes.



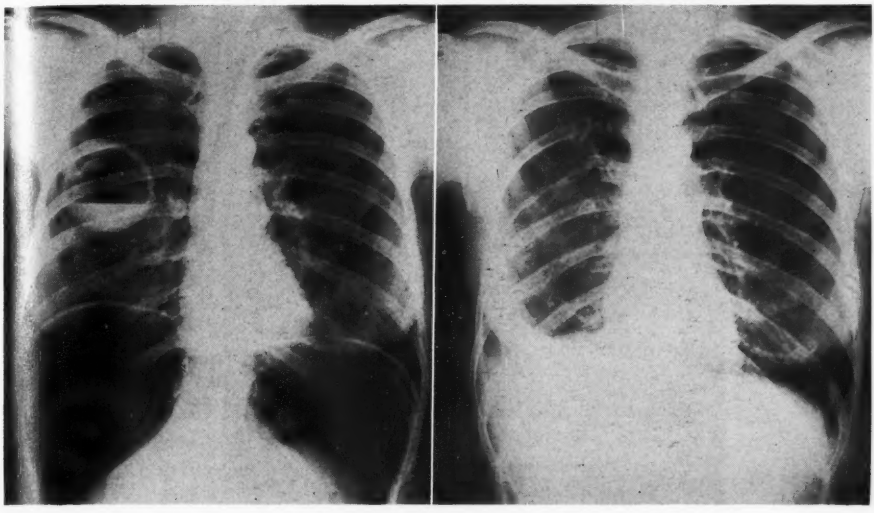
A. *B.*

Fig. 3 (Case 5).—*A*, Coccidioidomycosis cavity, left hilar area; *B*, coccidioidomycosis cavity secondarily infected with pulmonary tuberulosis.



A. *B.* *C.*

Fig. 4 (Case 8).—*A*, Cavity, under medical management, ruptured causing spontaneous pneumothorax with temporary bronchopleural fistula; *B*, coccidioidomycosis empyema with nonexpansile lung; *C*, preoperative, normal bronchial tree.

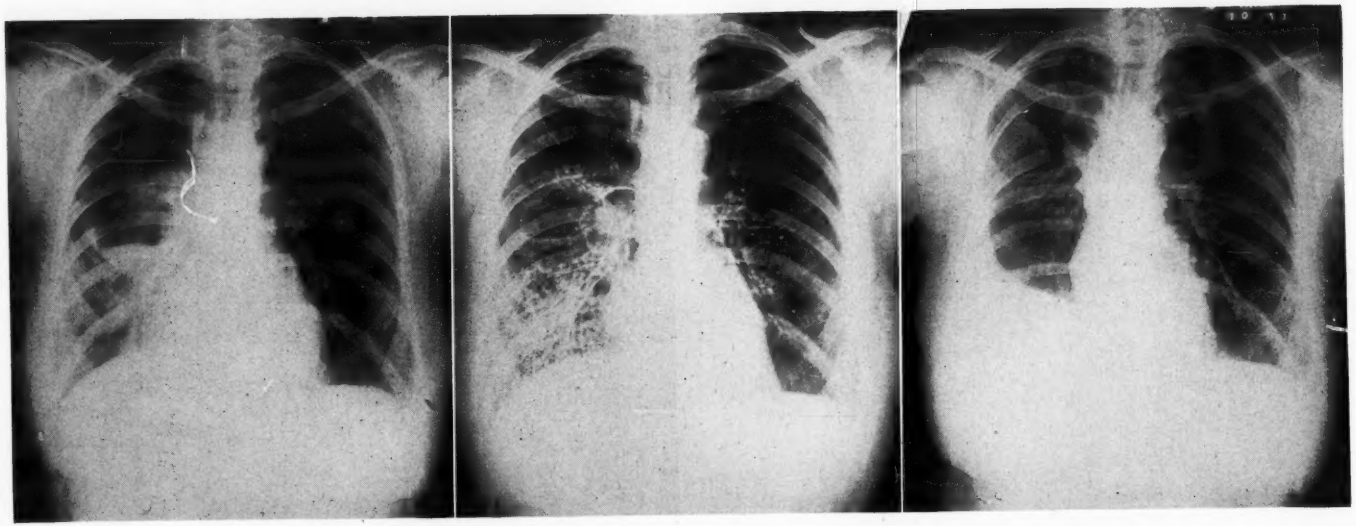


A. *B.*

Fig. 5 (Case 11).—*A*, Blocked cavity; *B*, postoperative.

A. *B.*

Fig. 6 (Case 16).—*A*, Cavitation, secondarily infected, associated primary carcinoma of the lung; *B*, postoperative.



A. *B.* *C.*

Fig. 7 (Case 19).—*A*, Large cavity, right lower lobe; *B*, bronchogram; *C*, postoperative.

more of the following conclusive laboratory methods: spherules in sputum; complement-fixation test; culture; guinea pig inoculation; and/or pathologic specimen. Five cases used in this series were included when they met the following criteria: typical history of acute pulmonary coccidioidomycosis, thin-walled cavity by roentgen examination, negative Mantoux and positive coccidioidin skin tests.

It is interesting to note that the diagnosis of coccidioidomycosis is occasionally easier to make in vivo than on examination of the pathologic specimen. The coccidioidal cavity, which in the acute phase allows recovery of the spherules from the sputum, may lose its identity in the presence of a superimposed infection of either tubercle bacilli or pyogenic organisms.

Types of operations employed in the series were:

1. Pneumonectomy	5
2. Lobectomy	11
3. Segmental lobectomy	8
4. Wedge resection with decortication	5
5. Decortication plus thoracoplasty	1
Total	30

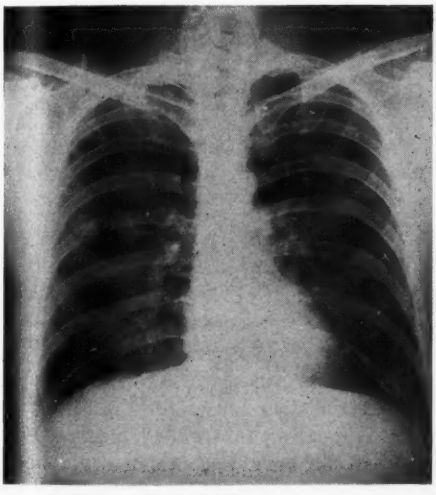


Fig. 8.

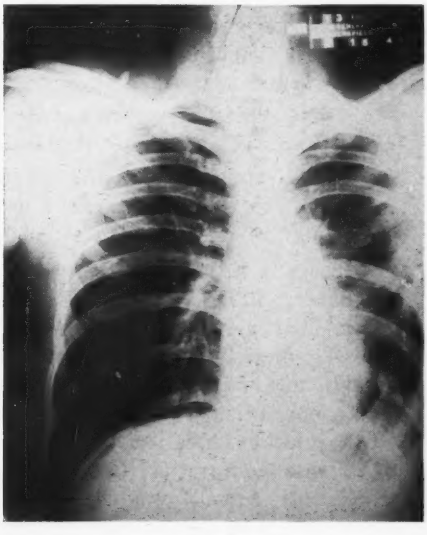


Fig. 9.

Fig. 8 (Case 21).—Coccidioma.
Fig. 9 (Case 7).—Postoperative film following decortication.

Twenty-seven of the thirty patients underwent operations for cavities, only six patients received operations for empyema, five of which had cavity resections, and three operations were performed in order to rule out the presence of carcinoma. Case 16 had associated primary carcinoma of the lung. In Case

11, the rapid destruction of lung parenchyma under medical management made the operation an emergency. In Case 7, concern over surgical intervention was expressed by the medical department because the blood titer was in the dissemination range. Despite this fact, as well as the fact that a cavity was removed and a decortication performed in the presence of a coccidioidal empyema, no clinical dissemination occurred postoperatively and the titer fell. In Cases 2, 3, 5, and 13, resection was done under local anesthesia in order to avoid postoperative complications arising from drainage. Cases 5, 9, 13, and 29 were complicated by tuberculosis in addition to coccidioidomycosis. In Cases 2 and 3, voluminous sputum due to secondarily infected cavities was present. The only death in this series was due to a coronary occlusion several days following operation.

DISCUSSION

Statistically, pulmonary coccidioidomycosis may be considered a benign disease even in areas in which it is endemic. However, such statistics have little significance to the patient hemorrhaging from a coccidioidal cavity, to the patient with a secondarily infected cavity (lung abscess), to the patient with dyspnea from an unexpanded lung, or to the patient misplaced in a tuberculosis sanatorium. The inaccuracy of general statistics regarding pulmonary coccidioidomycosis is perhaps directly attributable to three factors:

1. No simple diagnostic test is readily available in areas in which the disease is endemic.

2. No clinical symptoms manifest themselves after the patient has left the endemic area with the result that the proper diagnosis frequently is overlooked.

3. The majority of extrapulmonary lesions warrant hospitalization and extensive laboratory procedures, thus overshadowing chronic pulmonary lesions which may be treated on an ambulatory basis.

There is little doubt that certain selected cases will respond to medical treatment. It has been unquestionably proved by Winn* that many cases of coccidioidal cavitation can be cured by collapse therapy. In our series of cases where medical treatment was employed, the results were unsatisfactory. The medical measures ranged from bed rest, phrenic nerve crush, pneumothorax and pneumoperitoneum to months of hospitalization in tuberculosis sanatoria. Postsurgical examination of the specimens revealed two causes for the failure of collapse therapy: (1) the cavity, although appearing thin-walled roentgenographically, actually was composed of a dense fibrinous wall which could be obliterated with difficulty by direct manual pressure; and (2) dense adhesions were present from the cavity wall to the thoracic cage. The rationale of surgical removal in such cases was clearly established. Although the records showed that operative procedures in instances of extrapulmonic infections of coccidioidomycosis usually had resulted in further spread of the disease process, the progressive deterioration of certain patients under medical management left pulmonary resection as the only means of arresting the disease.

*W. A. Winn, Springville, Calif., personal communication.

The remarkable recovery without complications which followed the initial operations in this series, coupled with the fact that decortication was performed in the presence of an active coccidioidal empyema with complete re-expansion of the lung, the wound healing by primary intention—these results led us to conclude that suitability for operation could be determined without regard to the etiological nature of the pathologic condition or whether the disease was in a dormant or active phase. Consequently, we disregarded all laboratory findings and viewed the complication of pulmonary coccidioidomycosis from the mechanical standpoint only. A close analysis of the data in Table I further substantiates our conclusion that the medical status of the disease has little effect on either the indications for operation, the choice of operative procedure, or the postoperative results. Only in determining the priority for the patient on the operating room schedule is the medical status of the disease significant.

SUMMARY AND CONCLUSION

1. A series of thirty cases of pulmonary coccidioidomycosis treated by surgical methods is presented.

2. Surgical treatment in pulmonary coccidioidomycosis can be used to prevent death and is effective in arresting the disease process.

3. Surgical treatment in pulmonary coccidioidomycosis does not cause dissemination of the disease to the skeletal or nervous system, but may even prevent dissemination.

4. Surgical treatment is definitely indicated in pulmonary coccidioidomycosis in the following conditions:

1. Specific types of cavities
   a. Giant cavity
   b. Secondarily infected cavity
   c. Blocked cavity
2. Rupture of cavity
   a. spontaneous pneumothorax
   b. empyema
3. Nonexpansile lung
4. Hemoptysis
   a. continued
   b. severe
5. Coccidioma—expanding lesion
6. Failure of medical treatment (collapse therapy, etc.)

5. Coccidioma, which is usually single but may be multiple, must be differentiated from a tuberculoma, hamartoma, and both primary and metastatic carcinomatous lesions.

6. Lung complications resulting from pulmonary coccidioidomycosis should be evaluated surgically from the standpoint of pathologic lesions without regard to the fungus origin or activity of the disease.

7. Surgical treatment in selected cases of pulmonary coccidioidomycosis results in rapid rehabilitation of the patient.

8. The combination of pulmonary cavities due to tuberculosis and coccidioidomycosis does not constitute a contraindication to surgical management.

DISCUSSION

DR. W. L. ROGERS, San Francisco.—I have followed Dr. Cotton's work with a great deal of interest and I am sure you will agree that after this excellent report, which I believe represents the largest surgical experience reported to date in dealing with the complications of pulmonary coccidioidomycosis, together with the excellent report by our Denver colleagues as a result of their experience at Fitzsimons some two years ago before this organization, we are able to crystallize very well indeed our thinking in dealing with these complications. In the résumé, I believe point number six covers it very well. Lung complications resulting from pulmonary coccidioidomycosis should be evaluated surgically primarily from the lesion in question and the symptoms thereof, without regard to the specific fungus origin or perhaps the activity of the disease. This statement appears to me to be of primary significance while the surgical approach or technique used in the individual case may be considered quite secondary.

In our small series we have used lobectomy, wedge excision, decortication on the visceral pleural surface and, in four instances which may be of interest and sufficiently significant to relate, we have done a simple enucleation of the residual cavity. In each of the four cases the presenting symptom was repeated hemoptysis, a symptom mentioned by Dr. Cotton in some cases with a residual cavity. The existing pathology in each instance was a thin-walled cavity superficially located. In two instances, because of an incomplete fissure between the apex of the lower lobe and the inferior posterior segment of the upper lobe, the cavity transcended into two lobes. Very simply these cavities could be enucleated, vessels and small bronchi being ligated as encountered, and the defect created left open. Bearing in mind the importance of rapid expansion, especially when dealing with specific infections, we have utilized low-grade suction postoperatively in all these cases without encountering any trouble with the pleura.

I think it also highly important that in no instance was there clinical manifestation of reactivity, x-ray manifestation of activity, or serologic manifestation of reactivity in any of these people so treated. This last statement also applies to our other cases treated perhaps in a more orthodox manner.

COL. JAMES H. FORSEE, Denver.—Two years ago we reported before this Association our experience at Fitzsimons Hospital in the management of 13 patients with pulmonary coccidioidomycosis with focalized lesions. In view of Dr. Cotton's splendid report it may be of interest to note the follow-up studies on the 13 cases.

Four patients had granulomatous lesions removed and all have remained well. Nine patients had lobectomies performed for cavitary lesions. One patient developed pulmonary tuberculosis. After a review of the surgical specimen removed there was no evidence of tuberculosis present in this lung. Two patients are salesmen (one on a half-day basis), four are doing active military duty, two have been for the past year and one-half actively engaged as truck drivers.

We have continued to recommend pulmonary resection in coccidioidomycotic cavities if there are symptoms. These symptoms, as mentioned, are generally hemoptysis and pain. Our results so far, we believe, have been reasonably satisfactory, but we are not at all sure that the complete answer has been given in the treatment of cavities by lobectomy or pulmonary resection. We believe, however, at the present time, that this is the best method of management of persistent cavitation.

DR. JOSEPH A. WEINBERG, Van Nuys, Calif.—There is one point that I feel should be brought out particularly in discussing surgical treatment of granulomatous or cystic coccidioidomycosis of the lung. One reason for feeling our way cautiously in applying surgery up to the present time is that we have known so little about why the disease sometimes manifests itself as a localized disease and at other times becomes a disseminating disease. Although not proved, it has been suspected that the trauma of surgery during the acute stage of high complement fixation titer might convert a localized lesion into a disseminating infection. This question assumes grave significance when it is considered that about one-half the disseminating cases are fatal. Therefore, it might be well, while we are feeling our way with surgery in the localized lesions, to limit ourselves to those cases with negative complement fixation and to those cases with low complement fixation in a phase of declining titer.

I would like to show one case of rather extensive surgery which probably would not have healed otherwise, at least not as quickly. (Slide.) In this case thoracoplasty was performed after drainage of an empyema which was secondary to a pulmonary lesion of the type Dr. Cotton has shown. This slide shows the persistent space after thoracoplasty; even further thoracoplasty failed to heal the empyema or the multiple fistulas associated with it. The next slide is after extrapleural pneumonectomy, that is, pneumonectomy with decortication. Following this procedure the empyema together with the multiple fistulas healed. Convalescence was uneventful and the patient remains well today.

I have three slides from this case which may be of interest from the standpoint of histopathology. In this slide we see a sporulating granule lying free in the pulmonary tissue, with its double refractile membrane. The next slide shows a characteristic granule with epithelioid cells, giant cells, and a few leucocytes in the specimen. Here we see two empty sporules, showing that they are nonviable. The next rather interesting high power slide shows this giant cell apparently extending out pseudopodia-like processes to engulf the two sporules.

DR. COTTON (closing).—The chronic coccidioidal cavity should be included in the differential diagnosis of all chronic cavities. Modern day transportation has transformed an endemic disease into a pandemic disease. Widespread medical interest in coccidioidomycosis is manifested by more than 200 articles in the literature, with cases reported from the New England States to Argentina, South America.

Dr. Rogers has summed up the treatment of the chronic coccidioidal cavity very completely. It may be considered from the mechanical standpoint alone, and the disease process itself can be disregarded when the patient needs definitive surgical treatment.

PECTUS EXCAVATUM

Case Report With Pre- and Postoperative Angiocardiographic Studies

Ralph A. Dorner, M.D.,* Philip G. Keil, M.D.† (by invitation), and
Donald J. Schissel, M.D.† (by invitation)
Des Moines, Iowa

A NUMBER of authors[1, 2, 3] writing on the subject of pectus excavatum have questioned the existence of circulatory impairment from this deformity. Evans,[3] summarizing a study of 16 patients, aged 15 to 57 years (average age 24 years) stated, "It needs final emphasis that none of the 16 cases with depression of the sternum showed actual enlargement of the heart nor suffered from symptoms related to the heart. Indeed, they were all healthy and were handicapped only by the restrictions imposed on them by a medical examination that had misinterpreted the clinical and radiological signs." Steindler[4] concluded: "The operative elevation of the depressed sternum, as sometimes suggested, is a hopeless and unnecessary procedure." Sutton[5] feels cardiac disturbances do result from this deformity. The operative attack on the condition has continued.

Before The American Association for Thoracic Surgery, in 1938, Ochsner and DeBakey[6] reported a successfully treated case and presented an extensive review of the literature on this subject. The following year, Brown[7] suggested that the probable cause of pectus excavatum is anteroposterior shortening of the central tendon of the diaphragm. He presented surgical procedures for its prevention and alleviation. Sweet,[8] Ravitch,[9] Lester,[10] and others have attacked this problem applying the principles outlined by Brown. At the 1949 meeting Lester[11] reported 31 operated cases of thoracic cage deformities of diaphragmatic origin. Ravitch, reporting 8 cases in children 22 months to 10 years of age, listed the indications for surgery as (1) cosmetic, (2) orthopedic, and (3) physiologic. In these children cardiac disturbances were slight or absent. He concluded that surgical correction should be undertaken before general thoracic deformity or physiologic disturbances develop.

Most of the papers on this subject have dealt with surgical aspects of the problem, noting the fact that correction of the deformity was preserved and clinical improvement was maintained.

In this communication we wish to discuss a case of pectus excavatum having severe cardiac symptoms which were relieved by elevation of the sternum.

Sponsored by the Veterans Administration with the approval of the Chief Medical Director. Statements and conclusions published by the authors are a result of their own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

Read before the Thirtieth Annual Meeting of The American Association for Thoracic Surgery, Denver, Colo., April 15-18, 1950.

*Attending Thoracic Surgeon.

†Department of Internal Medicine, Veterans Administration Hospital.

CASE REPORT

History.—L. S., a 28-year-old white male carpenter, entered the hospital April 11, 1949, complaining of palpitation (eighteen months' duration) and a chronic productive cough (six years' duration). Funnel chest deformity had been present since the age of 9 months. For eighteen months prior to hospitalization the patient had episodes of rapid regular heart action associated with weakness, dizziness, precordial pain, dyspnea, and sweating.

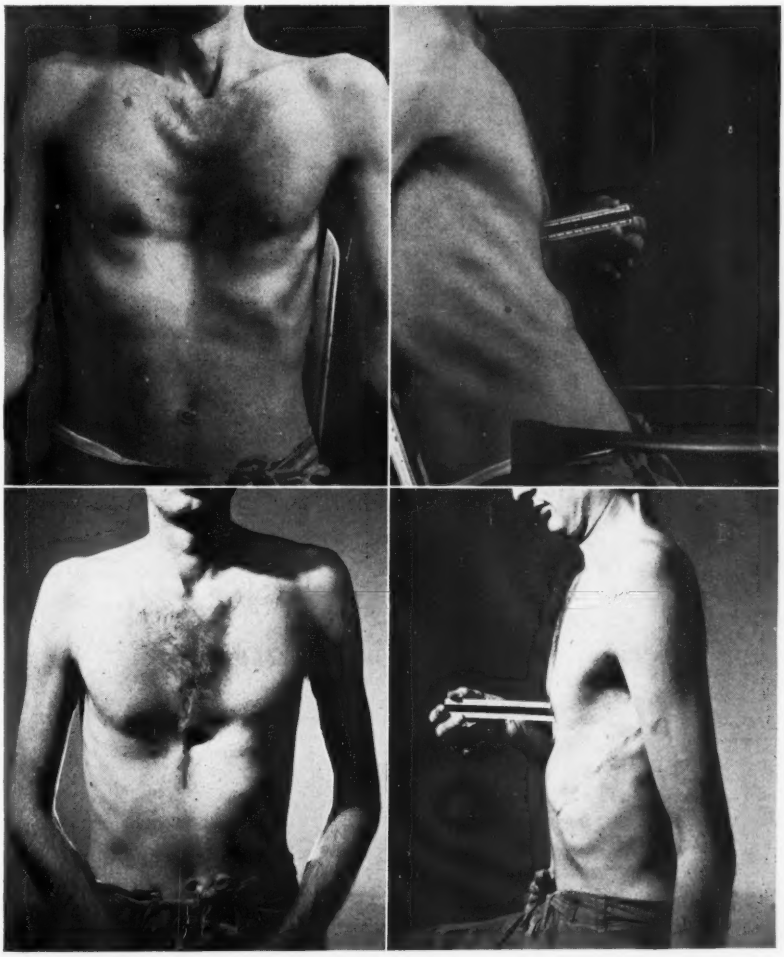


Fig. 1.—Anterior and lateral views of the chest, preoperative and postoperative.

The attacks occurred at irregular intervals, began and stopped suddenly, were produced by exertion and relieved by rest. They lasted two to fifteen minutes. During the attacks the pulse seemed regular but the rate increased to about 200 beats per minute. These episodes of tachycardia increased in severity and duration until two months prior to admission when slight exertion, such as assuming a standing position, initiated an attack.

The patient gave a history of moderately severe bronchiectasis for 6 years. There was no family history of funnel chest deformity. His father and mother were in good health and seven brothers and sisters were alive and well. The patient had lived a normal boyhood and was a distance runner on the high school track team. He was discharged from the army after eight months' service because of bronchiectasis.

Physical Examination.—The patient was 73 inches tall and weighed 136 pounds. The chest was long and thin and the lower sternum with adjoining cartilages was depressed two inches (Fig. 1). This depression held 300 c.c. of water. The trachea was in the mid-

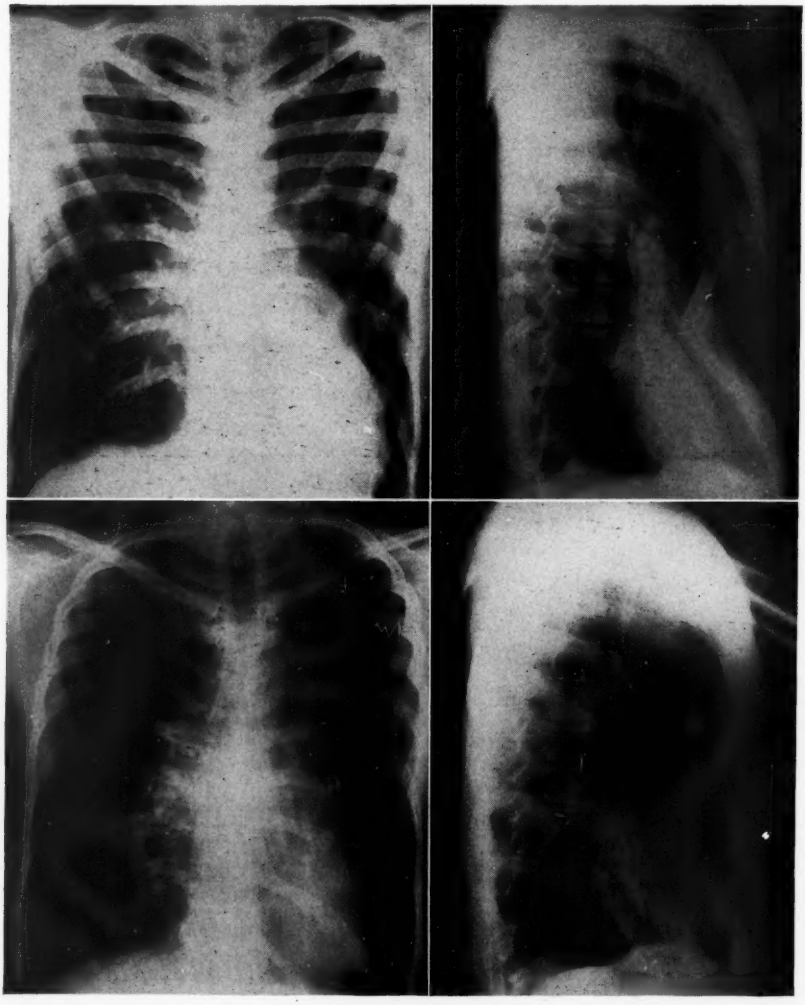


Fig. 2.—Posteroanterior and lateral roentgenograms of the chest, preoperative and postoperative. The normal dorsal curvature of the spine is absent. Clearance between the tip of sternum and the anterior surface of the vertebral bodies is one and three-fourths inches preoperatively and three and on-half inches postoperatively. Recession of sternum has not occurred by nine months after elevation.

line. The costal excursions were symmetrically limited. The normal curvature of the dorsal spine was absent. Expiratory wheezes were heard over the entire chest and coarse moist râles and rhonchi were present in both bases. The expiratory phase was prolonged. The heart was displaced to the left. The left border extended to the midaxillary line. The right border could not be localized. The heart tones were increased in intensity and there was a loud rumbling systolic murmur heard best in the fourth interspace to the left of the sternum. Blood pressure was 115/70. The heart rate varied from 68 at rest to 204 after minimal exertion.

Laboratory Examinations.—Urinalysis and complete blood count were normal. Serology was negative. The basal metabolic rate was plus 6. Sputum showed gram-positive cocci and numerous diphtheroids.

Posteroanterior and lateral chest roentgenograms showed marked indentation in the lower portion of the sternum and adjacent cartilages producing a marked funnel-shaped chest. The heart and mediastinum were displaced to the left (Fig. 2).

Bronchographic and bronchoscopic examinations revealed bilateral far-advanced bronchiectasis, most marked in the right middle and lower lobes.

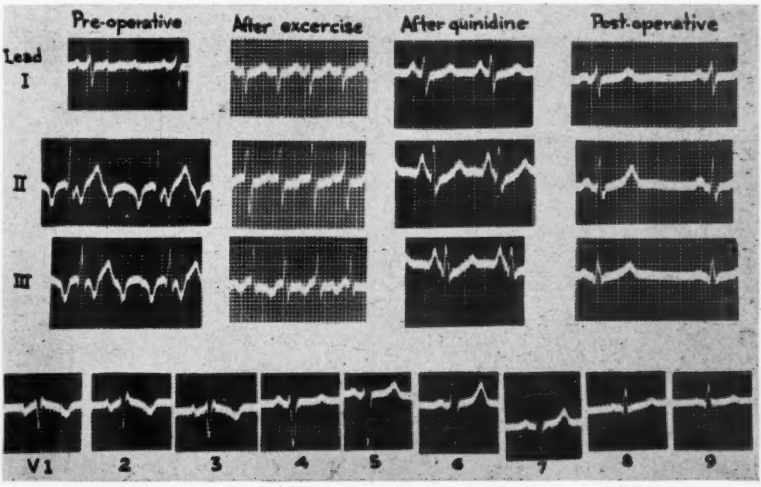


Fig. 3.—The electrocardiogram taken preoperatively under basal conditions (column 1) showed an auricular tachycardia with 3:1 auriculoventricular block, and deep, peaked inverted P waves in Leads II and III. A right heart strain pattern was present. After exercise (column 2) the block became 1:1 with a ventricular rate of 187. After the administration of quinidine (column 3) the rhythm became sinus and the right heart strain pattern persisted. Giant peaked P waves were striking.

Postoperatively the electrocardiogram became normal (column 4). The strain pattern disappeared. The P waves returned to within normal limits. The ventricular rate averaged 54.

"V" leads 1 through 9 before and after surgery were normal with the exception that they showed the heart to be definitely displaced and rotated to the left, the transition zone (septum) being at V_5 and V_6 (normal V_2 and V_3).

Hospital Course.—

Preoperative: Electrocardiograms showed the presence of a persistent supraventricular tachycardia with a varying block of 5:1 to 1:1 (Fig. 3). The 1:1 response occurred after minimal exertion and simulated the episodes of palpitation recorded in the history. After two weeks observation without change in the cardiac status, small doses of quinidine (0.2 Gm. every four hours) were administered orally and the rhythm reverted to normal after 0.6 Gm. However, the tall peaked P waves and the right heart strain pattern per-

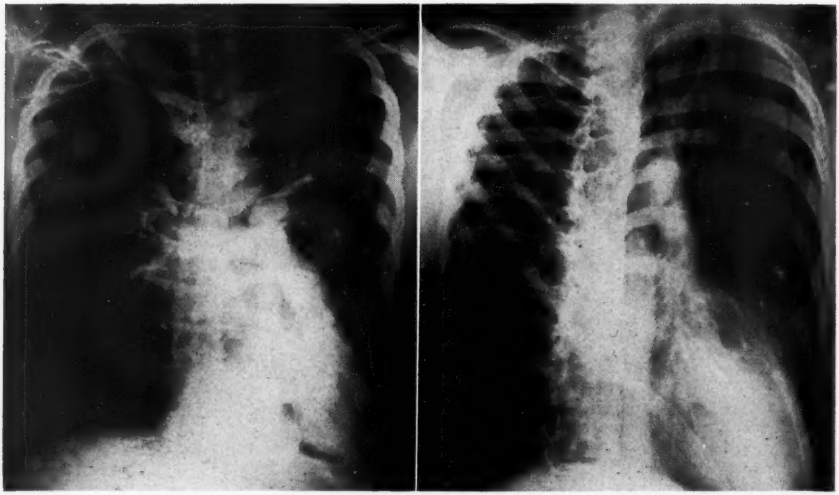


Fig. 4.—Angiocardiogram on the left taken in the posteroanterior position two seconds after rapid injection of 50 c.c. 70 per cent Diodrast into an antecubital vein. The superior vena cava is displaced to the left. The right atrium and ventricle are markedly dilated. The pulmonary artery makes up part of the left heart border. The angiocardiogram on the right was taken ten seconds after injection, in the left anterior oblique position. It shows a small posteriorly located left ventricle and hypoplastic aorta.

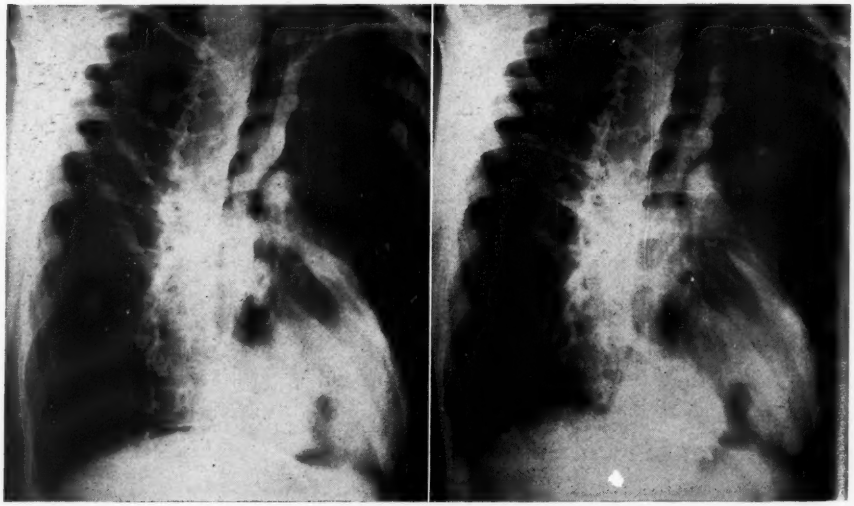


Fig. 5.—Preoperative angiocardiograms of the lesser circulation in the left anterior oblique position, taken four (left) and six (right) seconds after injection. The tricuspid valve ring appears distorted. There is obstruction to outflow of blood from the right atrium, which is normally free of dye on the four-second film.

sisted. The patient was dyspneic at bed rest before and after quinidine. He was raising 10 ounces of bronchiectatic sputum in twenty-four hours. During this time, treatment of the bronchiectasis consisted of postural drainage and penicillin therapy.

Angiocardiographic examinations preoperatively. (Figs. 4 and 5) showed marked enlargement of the right atrium and ventricle. The tricuspid valve ring was distorted. Dye puddled in the atrium, and circulation to the right ventricle was delayed. The greater circulation was normal. The aorta appeared somewhat hypoplastic.

Operative Procedure: On July 19, 1949, under nitrous oxide endotracheal anesthesia supplemented by sodium pentothal, a straight incision was made from the suprasternal notch to below the xyphoid. The skin, subcutaneous tissues, and pectoral muscles were reflected laterally on either side to beyond the costochondral junction from the second rib downward. The second to fifth cartilages (inclusive) were resected subperichondrally from sternal attachments to costal junctions, and the fused cartilages were divided. The intercostal muscles were left intact. The diaphragm was released by separating the xyphoid from the gladiolus, severing the substernal ligament. The sternum could then be brought well forward without dividing the manubrium and gladiolus (as recommended by most authors).

Fig. 6.—Angiocardiograms of the lesser (left) and greater (right) circulation three weeks after elevation of the sternum. The right atrium is considerably smaller and the circulation time is normal.

The xyphoid was allowed to drop posteriorly with the abdominal muscles and lower cartilages. A 10-inch segment of the left ninth rib was then resected subperiosteally and passed behind the sternum through the fourth cartilage spaces. When the rib was turned with its convexity anteriorly an over correction was obtained. However, when turned with its concavity anteriorly, the cosmetic effect was satisfactory.

After obtaining cancellous bone contact, the rib strut was anchored to the fourth anterior rib stump on either side with two interrupted sutures of No. 26 steel wire. With this fixation there was a tendency to spread the rib cage more widely, reducing the inversion of the distal portions of the ribs. The wound was flushed with normal saline and closed in layers without drainage after topical application of 300,000 units of penicillin into the mediastinal tissues. No. 35 stainless steel wire sutures were placed in the fascia

of the pectoral muscles as they were approximated. The skin and subcutaneous tissues were closed with interrupted sutures of similar material. The rib resection defect was closed with interrupted silk sutures. The operative time was two hours.

Postoperative: On return from the operating room, the patient was awake, the heart rate was 72, and the blood pressure 110/70. He was ambulated on the second postoperative day. The wound healed by primary intention.

Electrocardiograms obtained during the operative procedure showed diminution in the height of the P waves. The electrocardiogram taken the second postoperative day showed the right heart strain pattern had entirely disappeared and the P waves were normal.

Angiograms taken three weeks after operation showed (Fig. 6) the right atrium diminished considerably in size and the delay in the transit time of blood through the right atrium and tricuspid valve completely alleviated. Subjectively the dramatic response to sternal elevation paralleled the objective findings.

All studies have been repeated up to nine months postoperative and have remained within normal limits. The sternal depression now holds 30 c.c. of water. The murmur has disappeared.

DISCUSSION

Prior to elevation of the sternum, this patient was a cardiac cripple. The slightest exertion provoked tachycardia and incapacitating dyspnea. There had been no congestive failure. The type of arrhythmia, that is, supraventricular tachycardia with a varying degree of auriculoventricular block (5:1 to 1:1), is uncommon. The tachycardia had apparently been present for eighteen months and the degree of block varied with the patient's activity. The dynamics of the circulation were altered by delay of blood flow through the right atrium and tricuspid valve. This was obviated after sternal elevation. Disappearance of the murmur suggests that it had been due to distortion of the tricuspid valve. The previously conspicuous right heart strain pattern disappeared. Angiocardiograms obtained about three weeks after surgery showed considerable diminution in the size of the right atrium and a normal transit time of blood through the right heart. Postoperative exercise tolerance tests (Master's two step) were normal, in contrast to inability to carry out exercises preoperatively. The electrocardiogram became normal and has remained normal. In the nine months since surgery, there has been no recession of the sternum. Circulatory dynamics are normal. Though the heart size has diminished, the mediastinum is still shifted to the left and the transition zone is still V_5 to V_6 electrocardiographically.

SUMMARY

1. A case of severe funnel chest in a 28-year-old man with incapacitating cardiac symptoms and bilateral bronchiectasis is presented.

2. Detailed pre- and postoperative studies of the circulation bear out the premise that cardiac disability was due solely to impingement on the heart by the deformed sternum.

3. Results obtained by sternal elevation in this case substantiate the conclusions of Lester and Ravitch, who believe that surgical correction of severe or progressing deformities should be accomplished in childhood.

ADDENDUM

On June 5, 1950, a successful right middle and lower bilobectomy was performed for relief of this patient's bronchiectasis. The operative findings will be submitted for publication later.

REFERENCES

1. Teplick, J. G., and Drake, E. H.: Roentgen and Cardiac Manifestations of Funnel Chest, Am. J. Roentgenol. **56**: 721, 1946.
2. Edeiken, J., and Wolferth, C. C.: The Heart in Funnel Chest, Am. J. M. Sc. **184**: 445, 1932.
3. Evans, W.: The Heart in Sternal Depression, Brit. Heart J. **8**: 162, 1946.
4. Steindler, A.: Diseases and Deformities of the Spine and Thorax, St. Louis, 1929, The C. V. Mosby Company, pp. 81-82.
5. Sutton, G. E. F.: Cardiac Anomalies Associated With Funnel Chest, The Bristol Med.-Chir. J. **64**: 45, 1947.
6. Ochsner, A., and DeBakey, M.: Chōnē-Chondrosternon, J. THORACIC SURG. **8**: 469, 1939.
7. Brown, A. Lincoln: Pectus Excavatum, J. THORACIC SURG. **9**: 164, 1939.
8. Sweet, R. H.: Pectus Excavatum, Ann. Surg. **119**: 922, 1944.
9. Ravitch, M. M.: The Operative Treatment of Pectus Excavatum, Ann. Surg. **129**: 429, 1949.
10. Lester, C. W.: The Surgical Treatment of Funnel Chest, Ann. Surg. **123**: 1003, 1946.
11. Lester, C. W.: Funnel Chest and Allied Deformities of the Thoracic Cage, J. THORACIC SURG. **19**: 507, 1950.

DISCUSSION

DR. J. E. DAILEY, Houston.—I was interested in the technique used by Dr. Dorner in this case, and how nicely it turned out. Last year, in discussing Dr. Lester's paper on pectus excavatum, I presented a case with a new technique, that of elevation and fixation of the sternum by a rib graft. I did not report the case because there were some individuals who questioned whether the result would hold up over a period of time. My patient disappeared and it was only last month that I discovered where she was located, about 225 miles away. With the fine cooperation of a doctor there, who made some x-ray and electrocardiographic studies and obtained a photograph, I received the following slides. I would like now to show the results after two years.

(Slides.) This shows the patient before operation, the lateral roentgenogram showing the marked depression of the sternum. The next shows the immediate postoperative photograph, and the next was taken about one month after operation. The lateral incision is where a portion of the ninth rib was removed. After removing the cartilage around both sides of the sternum, the sternum was elevated and the rib placed across beneath it between the second rib on the right and the third on the left, and wired in place, thus acting as a bridge and supporting the sternum in its proper position.

The next slide is the lateral roentgenogram taken two years after operation, showing an excellent distance between the sternum and the spine. The next slide shows what has happened to the rib graft and I think you can see clearly where it has completely fused with the ribs on both sides of the chest.

I believe that this example thoroughly illustrates that this technique is practicable and that it will stand the test of time as well as if not better than some others.

We did not have the complete and beautiful cardiographic studies on our case that Dr. Dorner and his associates had. However, I might add that our patient showed a marked right axis deviation by electrocardiography and had the same cardiac symptoms as did his patient before operation. One month after operation the electrocardiograph showed improvement, and was perfectly normal at the end of two years.

DR. LAURENCE MISCALL, New York.—To the many methods that have been advocated, recently was added in the literature the possibility of fixation of the elevated sternum by the use of Kirschner wires. I would like to show you one case in which we have used it and permit you to draw your own conclusions as to whether or not it is advisable.

(Slides.) This little girl came to the New York Hospital because of severe respiratory difficulty, and constantly held her hands against her sternum to give some stabilization for respiration. Here is the posteroanterior view, March 7, 1949, showing distinct displacement of the heart to the left. The lateral view shows the depression of the sternum.

At operation we did what has been advocated generally; resection of the costochondral junction with elevation of the sternum. This was fixed by the criss-cross insertion of two pieces of Kirschner wire which were drilled across the sternum from the normal level of about the second rib diagonally into the end of the sixth rib of the opposite side. One wire was removed on the sixth postoperative day because it presented under the skin. The next slide shows the lateral postoperative view. The posterior curvature of the longer wire indicates the presence of definite tension on it. This was an excellent method of stabilizing the sternum and we were quite satisfied with it at the time of operation. The patient made an uneventful recovery.

(Slide.) This roentgenogram was taken in early August, when the girl was at the beach with her family. To this time it was a very beautiful case presentation illustrating the use of a new method.

However, in October the child returned to the New York Hospital with the story from her mother that she had had whooping cough. She had absolutely no symptoms. When this patient was fluoroscoped, in full expiration the wire picked up the motion of the heart. I think you can see the evidence of pericardial effusion and the position of wire in this plate. It was necessary to approach this through the left pleural space in order to keep away from the previous repair of the sternum. We removed this foreign body from the child's pericardium which contained a large amount of blood.

I think you can draw your own conclusions as to whether you wish to place and leave such wires in a child's sternum.

DR. CHARLES W. LESTER, New York.—I have been very much interested in this demonstration of Dr. Dorner's, about the cardiac disability that occurs in cases of funnel chest. I am firmly convinced that all patients who have any degree of depression of the sternum, have some cardiac disability. This is manifest first by the fact that they are nearly all underweight, underdeveloped, and show the general condition of individuals who have chronic heart trouble. In the second place, they do not know that their heart action is restricted because they have never experienced normal heart action. They tell you they are all right before operation, but after operation they note a marked improvement. Of course in a case such as Dr. Dorner showed there is no question about the damage to the heart, and that is true in any case of marked depression. I have never known before what the mechanism was. We have made many electrocardiograms and they have never been distinctive; they show right axis deviation for the most part and many show abnormalities which the cardiologist cannot interpret.

Many of these children, and adults as well, are bothered by cough. Some go on to the extent of severe bronchiectasis, and at least three in my experience have had tuberculosis as well. I think this is probably due to the fact that the cough is ineffectual because of the narrow diaphragm. I thought at one time it might be due to a kink in the bronchus, but I think shortening of the diaphragm explains it better.

So far as the appliance goes for keeping the sternum up in place, the graft of a rib is a very ingenious method. However, I think that the ladder as originally described by Brown eleven years ago, if it curved somewhat, is the most satisfactory. The wires can be taken out completely, nothing is left in, and the sternum is nicely brought up. In most cases, especially if the patients are fairly young, that is, before the age of 5 years, there is no deformity that can be seen later on. In the older patients there may be some residual deformity which is proportional to the amount of irreversible deformity present at the time of operation.

DR. A. LINCOLN BROWN, San Francisco.—Dr. Dorner's case presentation certainly confirms the fact that there are cardiorespiratory changes in every case of funnel chest. Last year we suggested that we wished to get information by cardiorespiratory studies, as to when operation might be advisable and what, if any, results other than structural were obtained by operation. The first three cases studied indicated in the first place that there was reversion of improvement; in other words, a certain amount of improvement is noted after operation in the cardiorespiratory mechanism, but after about three weeks approximately 50 per cent of that improvement was lost. We tried to reason why. We believed it was due to the fact that we had made a fixation of the chest. That seemed to be the only thing that can happen in three weeks' time. During the first three weeks the chest is unstable and a certain amount of increased respiratory motion is present but, after that, organization and regeneration take place and fixation ensues, whereby some of the improvement is lost. Since then, no fixation of any kind has been used except the one at the proximal end of the sternum to elevate it. In fact, there has been intentional freeing of the rest of the thoracic cage to allow for increased respiratory motion to continue. Regeneration, so far as cartilage goes, is prevented. In these cases the improvement that took place, such as it was, has persisted.

One of the simplest of all tests to determine cardiorespiratory embarrassment is that of maximal breathing capacity. Preoperative studies show the great majority of our adult patients with funnel chest to have a maximum breathing capacity of less than 50 per cent of normal. Improvement in maximal breathing capacity after operation, approximately 35 per cent. In 11 cases, preoperatively we have found that 9 had definite symptoms; 8 of these cases showed variable abnormal electrocardiographic findings. These do not take into account axis deviation, which is practically to be expected as normal in these individuals. But the other abnormal changes all terminated, if they went long enough, in cor pulmonale. Postoperatively, we had 6 cases followed over twelve months with cardiorespiratory studies; 5 were improved, 1 was the same. Five showed an increase in maximum breathing capacity averaging 31 per cent, 1 was unchanged, and in all the electrocardiogram has remained essentially unchanged.

DR. DORNER (closing).—I feel very humble this afternoon. Most of what I know concerning pectus excavatum has been learned from the discussors of my paper. I should like to give Dr. Dailey credit: Last year I heard him report the use of a rib strut and it was because of this that I used a rib in our case. I would like also to acknowledge the fact that my co-authors were responsible for the clinical work-up of our case as described.

I think Dr. Miscall should be congratulated. The response of the audience to his remarks shows how much we appreciate an honest report whether the case turns out well or badly.

The only thing I can say about follow-up in our case is that angiocardiograms and electrocardiograms taken very recently show the continued improvement that we noted on the earlier slides.

In closing, I would like to thank the discussors for their remarks.

SURGICAL TREATMENT OF CORROSIVE STENOSES OF THE THORACIC PART OF THE ESOPHAGUS BY A SINGLE-STAGE PALLIATIVE ANASTOMOSIS

Intracervical Retrovascular Anastomosis Without Resection of the Esophagus

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IN THE treatment of corrosive strictures of the esophagus which fail to respond to dilatation, re-establishment of the continuity of the gastrointestinal tract can be accomplished by different methods. The reconstruction can be carried out within the thorax or on the chest wall. In the antethoracic reconstruction the major part of the esophagus is left in situ, and the communication between the pharynx, or the intact portion of the cervical esophagus, and the remaining part of the gastrointestinal tract is made by means of cutaneous, intestinal, gastric, or mixed tube.[1, 2, 3, 4] Another method of antethoracic reconstruction for high lying, extensive, benign stenoses of the esophagus is done in two stages. At the first stage a subtotal resection of the esophagus is done followed by establishment of a cervical esophagostomy and of a gastrostomy. At the second stage the stomach is transplanted into a subcutaneous, antethoracic tunnel and an anastomosis made between it and the superior segment of the esophagus. This principle was first employed by Rienhoff,[5] and later by Bigger[6] in a case of congenital atresia of the esophagus when primary anastomosis was not feasible, and then by Taylor[7] for carcinoma of the esophagus.

One disadvantage of all antethoracic procedures is the necessity for multiple stages which so greatly prolong the period of treatment. However, the chief disadvantage is that there is such uncertainty as to the results obtained. One of us (V. R.) performed successful antethoracic reconstructions in three patients by the method of Wullstein-Lexer with the period of treatment lasting an average of nineteen months. Furthermore, in one of these it was necessary to reoperate five years later because of stenosis at the site of the jejunodermal anastomosis.[8]

ADVANTAGES OF INTRATHORACIC RECONSTRUCTION OF DIGESTIVE TRACT

In intrathoracic reconstruction of the digestive tract the result is obtained in a single stage. According to the extent and location of the stricture one of two methods may be used. In the first, resection of the stenosed esophagus and end-to-end anastomosis is done.[9] In this procedure in order to prevent tension on the suture line, mobilization of the esophagus[10, 11] or of the cardia of the stomach must be done.[5] In another group of cases it will be necessary to mobilize the stomach so that it may be partly, or completely, transplanted into the thoracic cavity for anastomosis to the proximal segment of esophagus after resection of the strictured part, or of it and part of the stomach.[12, 13] The

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mobilized stomach may also be anastomosed to the partly mobilized esophagus above the site of stricture without resection.[14] As yet it has not been decided whether it is better to resect the entire strictured part of the esophagus, or to be content with a palliative anastomosis and leave the esophagus in situ.

DISADVANTAGES OF RESECTION OF THE ESOPHAGUS

There are a number of disadvantages in resecting the involved esophagus. (1) First is the difficulty in mobilizing the esophagus due to the extensive fibrotic changes in the esophagus and around it. At times it is impossible to do a complete excision.[12] (2) In stenoses involving the mid-portion and the upper third of the esophagus, the mobilization of this structure and of the aortic arch is sometimes followed by functional disorders which may cause the death of the patient.[15, 16] Garlock blamed the stimulation of the vagus nerves. Nissen denied this[17] but mentioned the appearance of asthmatic attacks in one of his patients. (3) The isolation of the esophagus in the region of the azygos vein may cause troublesome bleeding from it. (4) Injury to the thoracic duct may be caused and overlooked, and thus lead to the death of the patient. (5) Radical resection of the esophagus entails resection of the vagus nerves and this causes atony and dilatation of the stomach which is badly tolerated, especially if the anastomosis must be placed high in the chest or in the neck. The dilatation of the stomach frequently leads to compression of the lung with subsequent atelectasis, dyspnea, and coughing. Even though the chief etiological factor in the production of an esophageal peptic ulcer is removed by vagotomy such ulcers can still develop, as shown by Allison,[18] who observed the formation of an esophageal peptic ulcer in a patient a short time after vagotomy had been done for a gastric ulcer, and in four other patients after resection of the cardia for cancer. (6) Resection with anastomosis is always a lengthy procedure, particularly when a subtotal resection of the esophagus is done.

ADVANTAGES OF RESECTION OF THE STRICTURED ESOPHAGUS

The main advantage of the radical procedure is that it eliminates the possible formation of carcinoma on the basis of the previous corrosive damage to the esophagus, as was reported by Benedict.[19] He reported sixteen cases of carcinoma developing on the basis of corrosive lesions of the esophagus without subsequent stenosis. However, this factor cannot always be completely excluded as in some instances small pieces of injured esophagus have to be left in situ. The second advantage of resection is the elimination of possible stagnation of food below the site of anastomosis. This danger can be minimized, however, by doing the anastomosis immediately above the highest point of the stricture. Another advantage of resection is that it does away with the possibility of an abscess developing in the vicinity of the remnant of the strictured esophagus that has been left behind. But this is of theoretical importance only, as the changes in the strictured area are mainly fibrotic in character. It may be thought that the end-to-side anastomosis guarantees a better, and more permanent, patency than does the side-to-side anastomosis, but we feel that this is not true when the procedure is carried out properly, and it has not been true

in our own experience. A definite answer to this particular point is not yet available. Finally, it is true that the end-to-side anastomosis is technically easier to perform than the side-to-side type.[12]

The feasibility of palliative side-to-side anastomosis in cases of stenosis of the middle and lower thirds of the esophagus is admitted by all. When, however, the stricture involves the upper esophagus the problem is far more complicated. Sweet[12] is of the opinion that a high anastomosis is not feasible without transection of the esophagus. We share this view in cases where the anastomosis is done by placing the stomach in front of the subclavian vessels.[20] If, however, contrary to Sweet's technique, the stomach is placed behind the vessels, the mere mobilization of the esophagus to the level of the aortic arch suffices for drawing the stomach into the neck and anastomosing it without tension. Because of these considerations, and as a result of our early success in the palliative side-to-side anastomosis for nonresectable carcinoma of the esophagus and cardia, we have decided to treat all our patients with corrosive strictures of the esophagus by this method.

In Table I is summarized our experience with seventy-two transthoracic operations for benign and malignant diseases of the esophagus, cardia, and stomach, during a period of somewhat less than three years. The marked difference in results from radical resection and from palliative anastomoses is apparent. Total gastrectomies were performed in twenty-four patients, twenty-three with carcinoma and one with a peptic ulcer. Four (16 per cent) of these

TABLE I. IMMEDIATE RESULTS OF TRANSTHORACIC OPERATIONS, RADICAL AND PALLIATIVE, FOR MALIGNANT AND BENIGN DISEASES OF THE ESOPHAGUS, CARDIA, AND STOMACH

OPERATION	NUMBER	DEATHS	
		NUMBER	PER CENT
Total Gastrectomy			
1. For peptic ulcer	1	0	0
2. For carcinoma of the stomach			
a. Simple: removal of both omenta and spleen	23	4	17.4
b. Combined: with resection of colon, pancreas, or liver	10	4	40
Total	34	8	23.5
Resection of Cardia and Esophagus			
3. For peptic ulcer of the cardia	4	1	25
4. For carcinoma of the cardia or lower fourth of the esophagus	17	6	35
5. For carcinoma of the middle part of the esophagus	3	0	0
Total	24	7	29
Palliative Anastomosis			
6. For carcinoma of the cardia and lower fourth of the esophagus	6	1	16.6
7. For carcinoma of the middle part of the esophagus	3	0	0
8. For benign stricture in the lower fourth of the esophagus	1	0	0
9. For benign stricture of the middle half of the esophagus	2	0	0
10. For stricture of the entire intrathoracic esophagus	2	0	0
Total	14	1	7.1

patients died. When resection of colon or pancreas was added to total gastrectomy the mortality rose to 40 per cent as four of the ten patients died. The combined immediate mortality for all total gastrectomies was 23.5 per cent. Resections were done in twenty-four patients for carcinoma of the cardia, and carcinoma of the esophagus. Seven of these died (29 per cent). Thus, of fifty-eight patients who were subjected to radical transthoracic resections for lesions of the stomach and the esophagus, fifteen died (26 per cent). Fourteen patients were treated by palliative transthoracic esophagogastrostomy, and only one died (7.1 per cent). These were done for nonresectable malignant stenoses of the cardia and thoracic esophagus, or for benign strictures of the thoracic esophagus.

Following these operations the patients are kept in the hospital for at least three weeks, as many of the common complications do not occur until after ten days. Sometimes at the beginning of the third week signs of leakage from the site of anastomosis appear, due to perforation of stitch abscesses, and later there develops mediastinitis and empyema. In Table I are included all deaths occurring in connection with the operations. The only death which occurred among the cases in which palliative anastomosis was done was in a man who had a stenosing carcinoma of the cardia involving the esophagus with metastases to the liver and peritoneum. It is felt that in this patient too much surgery was done.[21] However, we feel strongly that where radical resection can be done for carcinoma it should be done, even though the mortality rate is higher than for palliative anastomosis. In this opinion we differ from d'Allaines and Dubost.[23]

I. ESOPHAGOGASTROSTOMY WITHOUT RESECTION FOR CORROSIVE STRICTURES OF THE MID-PORTION OF THE ESOPHAGUS

Two patients with stenosis of the mid-portion of their esophagus resulting from the ingestion of lye were treated by esophagogastrostomy without resection of the esophagus. In both the stomach was mobilized through an abdominal approach, the right crus of the diaphragm divided, and then through a right thoracic approach a side-to-side anastamosis was performed.

CASE 1.—The first patient was a 30-year-old woman who had swallowed some lye, by mistake, ten years before being seen. Because of increasing difficulty in swallowing she had had a gastrostomy done nine years previously. Roentgen-ray examination revealed a stenosis starting somewhat above the level of the bifurcation of the trachea, and continuing down to the cardia. The stomach appeared to be normal. On April 28, 1949, operation was done under endotracheal, ether-oxygen anesthesia, supplemented by curare. Through a supraumbilical incision with resection of the xyphoid process, the gastrostomy was first closed and then, the stomach and lower 4 cm. of the esophagus were mobilized. The right crus of the diaphragm was divided obliquely, and the abdominal wall was then closed. The patient was then turned on the left side and the right pleural cavity entered through the bed of the sixth rib, which had been subperiosteally resected. A small paravertebral segment of the fifth rib was also resected. The phrenic nerve was not crushed. The azygos vein was divided and then the esophagus above the site of the stenosis was freed of overlying tissue but not mobilized. After division of the inferior pulmonary ligament, and of the mediastinal pleura, the lower 8 cm. of the esophagus was mobilized. The posterior wall of the mobilized stomach was then anastomosed to the anterior wall of the esophagus above the stenosis, and the

stomach anchored to the pleura and diaphragm. A rubber tube drain was placed into the pleural cavity through the ninth intercostal space, and the chest wall closed in layers. Recovery was prompt. Roentgen-ray examination on the fourteenth day after operation (Fig. 2) showed a well-functioning anastomosis at the level of the bifurcation of the trachea. There was evidence of slight hastening of the emptying of the stomach. On May 18 she was discharged as cured, being able to swallow solid food without trouble. By June 27 she had gained two kilograms in weight and had remained well.

Fig. 1 (Case 1).—Preoperative roentgenogram of stenosis of the middle half of the esophagus.

CASE 2.—The second patient was a 26-year-old woman who had swallowed lye, by mistake, thirteen years before admission to the hospital. Difficulty in swallowing had become so severe in a few weeks that dilatations of the esophagus had been started. These dilatations were continued at intervals, but during the last six months she had only been able to swallow semisolid food. She had lost ten kilograms in weight. Roentgen-ray examination showed the stenosis to be above the level of the bifurcation of the trachea with dilatation of the esophagus above it. On May 25, 1949, she was operated upon in a manner exactly similar to that used in the first case. Both the vagi and the phrenic nerve were preserved intact. Recovery was uneventful and she was discharged on the seventeenth day swallowing solid food without difficulty. Roentgen-ray examination revealed patency of the anastomosis.

DISCUSSION

As in carcinoma of the esophagus, so, with corrosive stenosis of the esophagus, the operative technique will vary with the location and extent of the stenosis. This is as true of the radical procedures as of the palliative anastomosis. For stenosis of the lower fourth of the esophagus there is no question about the advisability of the approach through the left chest. There is some question, however, as to whether it is better to use the stomach, or a jejunal loop as prepared by Roux and suggested by Allison.[24] The suggested advantage of using a structure nearer to the size of the esophagus for anastomosis to it, and the possible elimination of esophageal peptic ulcers by using the jejunal loop, are balanced or outweighed by the greater operative risk and the elimination of the stomach from the direct intestinal channel.

Fig. 2 (Case 1).—Postoperative roentgenogram of intrathoracic anastomosis through right thoracotomy taken fourteen days postoperatively.

In stenoses of the middle third of the esophagus there will be difference of opinion as to choice of approach. This will be particularly true when the stenosis starts immediately below the arch of the aorta, or behind and above it. When the anastomosis can be done below the arch of the aorta a left thoracic approach is to be preferred as it eliminates the need for a preliminary mobilization of the stomach through the abdomen. For anastomoses above the arch of the aorta we believe that transabdominal mobilization of the stomach according

to the technique of Macmanus, followed by a right thoracotomy will be better.[22] This has been our experience with palliative anastomosis in inoperable cases of carcinoma located behind and above the arch of the aorta. The right-sided approach allows easier access to the esophagus, avoids injury to the thoracic duct, and the damage to the diaphragm is minimized. In our opinion these advantages outweigh the disadvantage of the preliminary laparotomy.

II. INTRACERVICAL ESOPHAGOGASTROSTOMY

The indications for intracervical esophagogastrostomy are as follows: (1) Malignant growths in the upper fourth of the esophagus where intrathoracic anastomosis is not feasible because of the high location of the tumor, or where the neoplasm is located too low for the restoration of the alimentary canal by the method of Wookey. (2) In those congenital atresias of the esophagus where, after closure of the tracheoesophageal fistula, reconstruction of the continuity of the esophagus will be impossible and a gastrostomy and esophagostomy will be needed.[20] It is highly probable that the antethoracic implantation of the stomach into a subcutaneous tunnel as described by Rienhoff[5] will be safer. (3) Benign stenoses of the esophagus of cicatricial origin which affect practically all of the organ.

The first intracervical esophagogastrostomy, of which we know, was performed by Sweet in June, 1947. The patient was a 21-month-old child with a tracheoesophageal fistula which was closed at the first-stage operation, and at the second stage the anastomosis was completed. On Oct. 28, 1947, one of us (V. R.) had the honor of being present at an operation for carcinoma of the upper esophagus when Sweet performed a subtotal resection of the esophagus and a subsequent intracervical esophagogastrostomy. The patient made a prompt recovery. Soon afterward Garlock[15] published his technique for intracervical anastomosis after subtotal resection of the esophagus for carcinoma high above the aortic arch. His patient died on the second day after operation, probably as a result of profound functional changes due to stimulation of the vagus nerves. Subtotal resection of the esophagus is common to both methods, the principal difference being that in performing the anastomosis Garlock brings the stomach up behind the aortic arch and its branches whereas Sweet brings the stomach up in front of them. In both methods the vagi will be stimulated. Moreover, in Sweet's method there will be an additional stimulation of the periadventitious nervous plexuses, and perhaps even a stimulation of the carotid sinus. The tachycardia following change of position in Sweet's patient during the first four days after operation was ascribed to increased activity of the carotid sinus.

When considering the methods of single-stage operations which would be of the greatest advantage to our two patients with corrosive stenosis of the entire esophagus our aims were threefold. First, we wished to abandon the technically difficult and physiologically severe mobilization of the strictured esophagus with subsequent subtotal resection. Then we wished to transpose the mobilized fundus of the stomach behind the great vessels in the chest and in the neck, thereby

producing as physiologic a course for the new esophagus as possible. Finally we wished to reduce, as much as possible, the disturbances caused by neurovegetative stimulation. It was necessary, therefore, by studies on cadavers, to decide which anatomic structures are encountered during the performance of retrovascular transposition of the stomach.

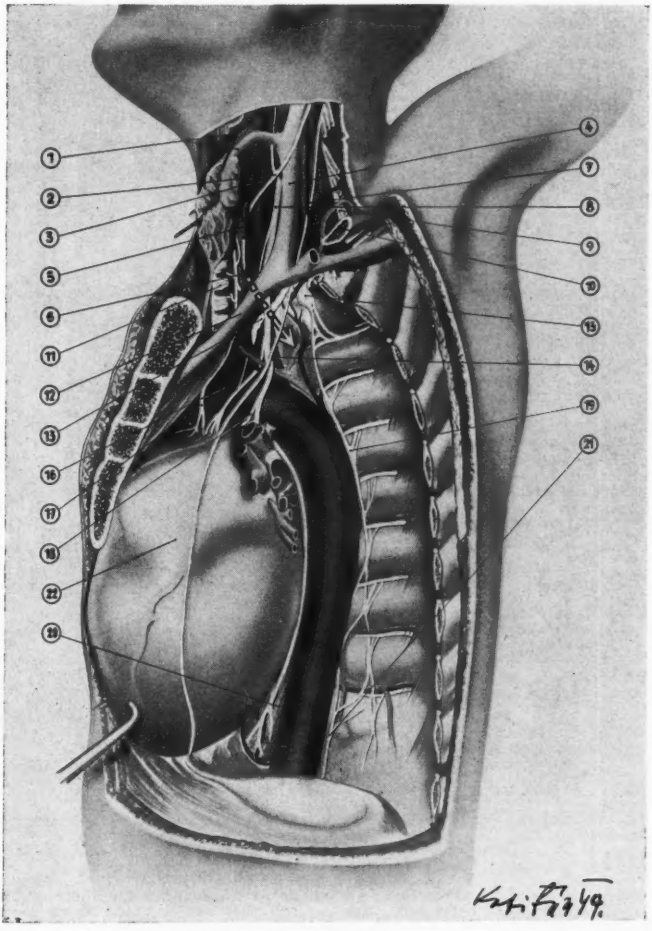

Fig. 3.—Illustrating the neurovascular cervical trunk and the mediastinal organs on the left side.

1, Superior thyroid vessel; *2*, ansa hypoglossi; *3*, common carotid artery; *4*, internal jugular vein; *5*, esophagus; *6*, recurrent nerve; *7*, phrenic nerve; *8*, vagus nerve with right cardiac; *9*, brachial plexus; *10*, clavicle; *11*, trachea; *12*, innominate vein; *13*, thoracic duct; *14*, esophagus; *15*, stellate ganglion; *16*, aortic arch; *17*, sympathetic cardiac nerve; *18*, recurrent nerve; *19*, truncus sympaticus; *20*, esophagus with left vagus nerve; *21*, major splanchnic nerve; *22*, pericardial sac.

ANATOMIC REMARKS

The structures which will be encountered during the preparation of the retrovascular tunnel in addition to the esophagus itself are: the thoracic duct, the stellate ganglion and its branches, the longitudinal septum, and the cover of the pleural dome (Fig. 3).

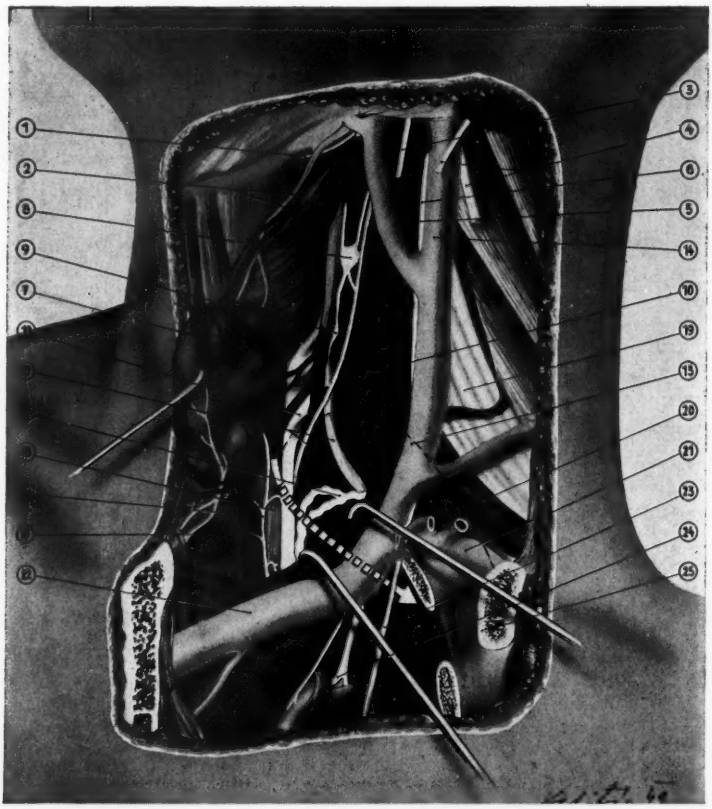

Fig. 4.—Showing the operative site on the neck. Neurovascular cervical trunk removed from the fibrous sheath.

1, Superior laryngeal nerve; *2*, superior thyroid vessel; *3*, right descending hypoglossal nerve; *4*, cervical plexus; *5*, common carotid artery; *6*, vagus nerve; *7*, thyroid gland; *8*, medial sympathetic ganglion; *9*, intermediate left ganglion; *10*, inferior thyroid artery; *11*, vertebral vessel; *12*, longitudinal septum; *13*, cupula of the pleura; *14*, internal jugular vein; *15*, esophagus; *16*, recurrent nerve; *17*, trachea; *18*, thoracic duct; *19*, brachial plexus; *20*, subclavian artery; *21*, subclavian vein; *22*, innominate vein; *23*, phrenic nerve; *24*, recurrent nerve; *25*, clavicle.

The thoracic duct runs first in the chest between the azygos vein and the aorta. At the level of the fifth thoracic vertebra, corresponding to the level of the bifurcation of the trachea, it crosses to the left side through areolar tissue behind the esophagus, and runs up posterior to the arch of the aorta and accompanies the left subclavian through the thoracic inlet into the neck. In the

neck the thoracic duct appears in the fissure between the common carotid and subclavian arteries, forming an arch with its convexity upward, and crosses in front of the subclavian artery, vertebral artery and vein, and the thyrocervical trunk or its branches, and empties into the vascular system at the angle of junction between the subclavian and internal jugular veins. In establishing the retropleural and retrovascular tunnel for the upward passage of the fundus of the stomach the thoracic duct and the entire neurovascular trunk are shifted together (Figs. 4 and 6).

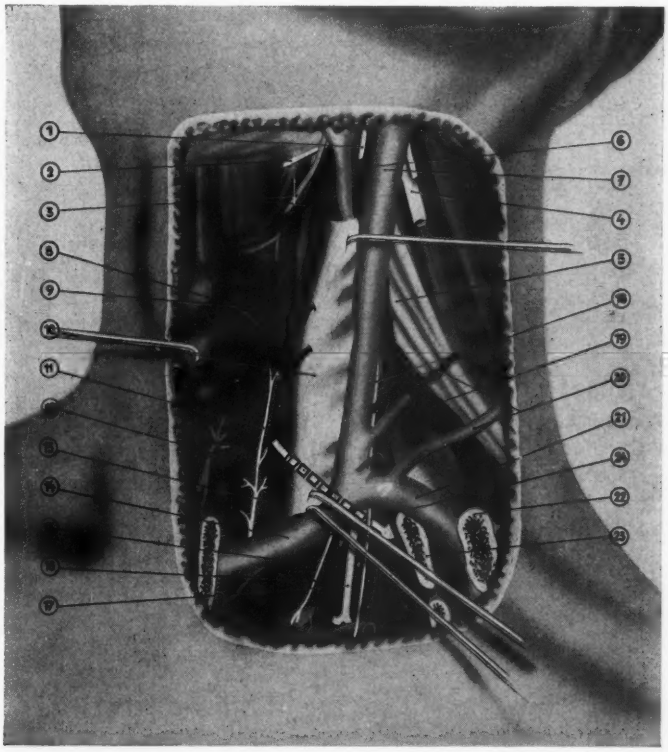

Fig. 5.—Showing the operative site on the neck. Neurovascular cervical trunk is covered from the medial side partially by the fibrous sheath. Arrow demonstrates the direction and the course of the retrovascular tunnel.

1, Right descending hypoglossal nerve; *2*, superior laryngeal nerve; *3*, superior thyroid vessel; *4*, cervical plexus; *5*, brachial plexus; *6*, carotid artery; *7*, internal jugular vein; *8*, thyroid gland; *9*, right inferior artery of the thyroid gland; *10*, longitudinal septum; *11*, recurrent nerve; *12*, trachea; *13*, esophagus; *14*, innominate vein; *15*, aortic arch; *16*, right cardiac vagus nerve; *17*, vagus nerve; *18*, phrenic nerve; *19*, subclavian artery; *20*, superficial cervical vessel; *21*, subclavian vein; *22*, clavicle; *23*, first rib; *24*, internal thoracic artery.

The stellate ganglion and the entire sympathetic trunk are not in immediate contact with the region of the retrovascular tunnel. Nor does the stomach, when anastomosed to the esophagus, come into direct contact with the ganglion and sympathetic trunk. The only structures that come into close proximity to the

operative site are the visceral branches of the stellate ganglion to the cupula of the pleura, the esophagus and trachea, and the inferior cardiac nerve. The inferior cardiac nerve first runs along the posterior aspect of the common carotid artery, then behind the arch of the aorta and on to join the cardiac plexus. As it is common for vegetative nerves to have anomalous courses, their fibers may be damaged by the pressure of the transposed stomach on the posterior aspect of the chest. Bruising these fibers might explain the tachycardia which was noted during the first days after operation, if this tachycardia were not simply due to the long and severe operative procedure.

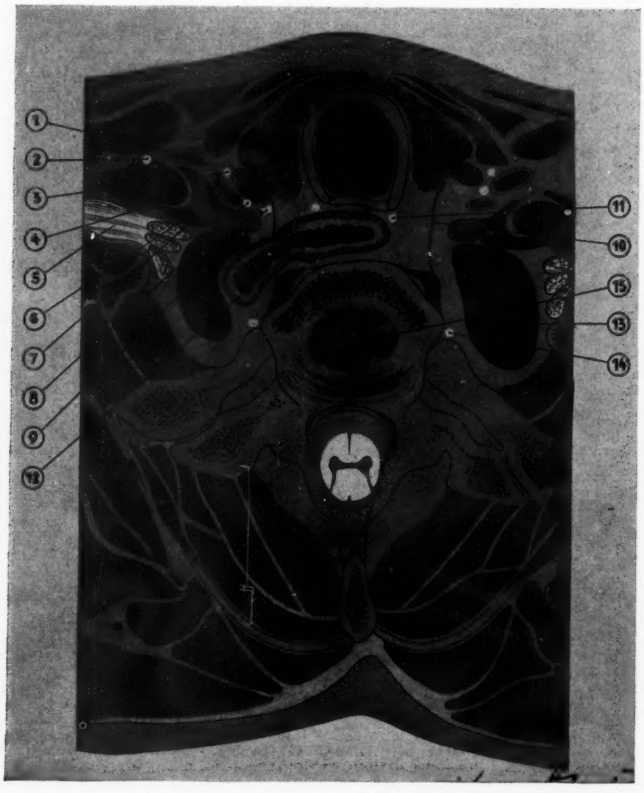

Fig. 6.—Section through the neck in the level of the anastomosis.

1, Left subclavian vein; *2*, phrenic nerve; *3*, right descending hypoglossal nerve; *4*, common carotid artery; *5*, brachial plexus; *6*, internal jugular vein; *7*, left subclavian artery; *8*, vagus nerve; *9*, thoracic duct; *10*, longitudinal septum; *11*, recurrent nerve; *12*, anastomosis between esophagus and fundus ventriculi; *13*, cupula of the pleura; *14*, truncus sympathicus; *15*, first thoracic vertebra.

The longitudinal septum (Figs. 5 and 6) is part of the connective tissue investment of the cervical neurovascular trunk. It is also most distinctly developed within the chest. In the neck it is formed by the pulsatory effects of

the carotid artery on the surrounding, originally structureless, connective tissue. The dorsal part of the septum which extends from the fibrous sheath to the prevertebral fascia, and the ventral part which is directed towards the middle cervical fascia, are considerably attentuated and may be altogether absent, particularly in the anterior portion. The middle part of the septum, which is the thickest, is pierced by branches of the inferior thyroid artery which pass to the thyroid gland or to the esophagus. The longitudinal septum extends inferiorly in the chest to become continuous with the suspensory ligament of the diaphragm. Like all cervical fascia, the longitudinal septum shows individual variations as far as its development and condensation are concerned, but it is well developed in the region of the neurovascular trunk and serves as a good protection against injuries during the preparation of the retrovascular tunnel (Fig. 6).

The cupula of the pleura reaches posteriorly to the neck of the first rib (Fig. 4). It is covered by a layer of connective tissue belonging to the endothoracic fascia, and is bridged by the suprapleural fascia of Sibson.

OPERATIVE TECHNIQUE

1. First step of the Operation: Thoracic procedure.—With the patient lying on the right side, left thoracotomy through the bed of the previously resected eighth rib is done. After resection of the intercostal nerve, the corresponding vessels are transfixed at both ends of the incision. After allowing the lung to collapse, 10 c.c. of 1 per cent procaine without epinephrine are injected into the pericardial sac. The same solution is used for infiltration of the thoracic sympathetic chain, the splanchnics, and the mediastinum. The inferior pulmonary ligament is divided and the bleeding points controlled by electrocoagulation. The mediastium is entered and the leaves of the pleura are reflected to allow visualization of the esophagus. By blunt, and, where necessary, sharp dissection the lower part of the esophagus is then delivered from the mediastinum.

After crushing the phrenic nerve for a distance of 2 mm. the diaphragm and esophageal hiatus are divided between transfixion sutures, after which clips are applied. This procedure facilitates the closure of the diaphragm after the termination of the thoracic stage of the operation. Before mobilizing the stomach the patency of the pylorus is determined. The stomach is then mobilized in the usual manner, preserving the right gastric and gastroepiploic arteries and leaving the spleen in situ.

After the stomach and cardia are freed the esophagus is mobilized to the level of the aortic arch. All bleeding is carefully controlled and injury to the vagus nerves is avoided. In our first case both vagi were severed as it was feared that intracervical transposition of the stomach could not be otherwise accomplished. In the second case only the anterior branch of the vagus could be identified but it was preserved. Through the wall of the fundus of the mobilized stomach are passed two guide sutures of silk, and then by means of a Reverdin needle they are brought out through the second interspace in the midclavicular line.

The next step is fixation of the stomach to the posterior chest wall with interrupted sutures. This is done by starting at the prepyloric part and proceeding upward to the fundus, anchoring the stomach along its greater curvature to the parietal pleura and along its lesser curvature to the mediastinal pleura. Fixation of the diaphragm to the gastric wall and closure of the diaphragm then follow. Before closing the thoracotomy wound a drain is placed in through the ninth intercostal space in the posterior axillary line.

2. The Second Step of the Operation: Intracervical Anastomosis.—The patient is placed on his back and about fifteen or twenty minutes are allowed for stabilization of the patient's pulse and blood pressure.

Fig. 7 (Case 3).—Incisions for the first and second steps of intracervical anastomosis.

Incision: The incision is made along the inner border of the sternomastoid muscle from the thyroid cartilage to the clavicle, the lower end of the incision being about 1 cm. lateral to the sternoclavicular joint. The incision is extended downward to the second intercostal space. Immediately above the upper border of the third rib the incision is curved slightly laterally to the point at which the guide sutures from the stomach emerge (Fig. 7).

Temporary resection of the clavicle and resection of segments of the upper two ribs. After preparation of the lateral musculocutaneous flap the clavicle is denuded and muscular insertions stripped. After dividing the sternal part of the sternomastoid muscle the clavicle is divided extraperiosteally with a Gigli saw at a point about 5 to 6 cm. from the sternoclavicular joint. In both of our cases we then dislocated the clavicle at the joint but we believe that it would be better to divide the clavicle outside the joint so as not to disturb it. The pectoralis major muscle is next divided along the course of its fibers, and then

after cutting the subclavian muscle and the costoclavicular ligament the divided clavicle, with its attached muscles, is easily reflected and the first two ribs are subperiosteally resected for 4 to 5 cm. In this way the reconstruction of the operative wound is considerably facilitated, and more perfect closure of the pleural cavity assured.

The approach to the cervical esophagus.—This does not differ from the current manner of operation. The recurrent branches of the vagus are identified and the short branches entering the wall of the esophagus are divided. The esophagus is then mobilized enough to allow the passage of a fine tape around it, thus facilitating the performance of the anastomosis without impairing its viability.

Opening the pleural cavity.—The pleural cavity is entered through the bed of the resected second rib and a perfect visualization of the various anatomic structures in the mediastinal and retropleural regions is obtained.

Preparation of a retrovascular tunnel.—Drawing the neurovascular trunk invested by its sheath and reinforced by the longitudinal septum, gently outward, the left index finger penetrates through the periesophageal areolar tissue, remaining constantly in contact with the outer wall of the esophagus. This is usually done without encountering much resistance. More pronounced resistance is noted at a point where the longitudinal septum and Sibson's fascia are continuous with the prevertebral fascia, but it is easily overcome. The finger penetrates further with the back of it in contact with the posterior chest wall. When the finger has been forced up as far it can reach a slightly curved hemostat with blunt tips is introduced into the tunnel and by opening and closing it the tunnel is dilated up to the posterior aspect of the subclavian artery where the pleura is torn with the tips of the instrument. The opening in the pleura is made about 3 cm. in length.

Intracervical anastomosis.—Into the prepared retrovascular tunnel, which will admit two fingers comfortably, the stomach is drawn by means of the guide sutures into the neck wound. The anastomosis between the stomach and the anterior wall of the esophagus is done with two layers of interrupted sutures, care being taken to get perfect mucosal approximation. The esophagus is incised obliquely so that the line runs downward and medially. The length of the incision must vary with the size of the esophagus. An attempt is made to place the lower pole of the anastomosis immediately above the area of stenosis. This step is important as it helps to prevent the formation of a cul-de-sac which becomes inflamed and endangers the patency of the anastomosis. The site of stenosis is localized by passing a Levine tube down the esophagus before the incision is made. After finishing the anastomosis the anterior wall of the stomach is sutured to the esophagus above the site of anastomosis with two sutures.

Reconstruction.—The pleura is closed with a fine continuous suture which also includes the periosteum. The clavicle is then reunited and held in place with wire. In our two cases after placing the clavicle in position the capsule of the sternoclavicular joint was closed with silk sutures. The divided sternal

part of the sternomastoid muscle is sutured and the pectoralis major muscle reunited. The closure of the wound is completed without drainage. The lung is then re-expanded after the injection of 25,000 units of penicillin and 0.5 Gm. of streptomycin into the pleural cavity and the tube drain into the cavity closed. The final step is the performance of a paravertebral block.

Fig. 8 (Case 3).—Preoperative roentgenogram of high stenosis of the esophagus.

Postoperative treatment.—This does not differ from the postoperative treatment after resection, or palliative anastomosis, for carcinoma of the esophagus or cardia. Twelve hours after operation the patient is started on clear tea, 30 c.c. every two hours. The quantity of fluid is gradually increased so that the patient is taking liquids freely on the fourth day. After the sixth day he is given semisolid food which is always followed by tea. At the end of a fortnight the patient is on full diet.

The fluid in the thorax is evacuated every twenty-four hours. As soon as the fluid stops forming and the lung has re-expanded the drain is removed. In the first case this was done on the second day, and in the other case it was done on the third day. After aspiration of the pleural fluid there is always injected into the thorax 25,000 units of penicillin and 0.5 Gm. of streptomycin.

Pain is relieved by paravertebral block. Recently we have obtained good results with a drip infusion of a 0.2 per cent solution of procaine in 5 per cent dextrose as described by Brittain.[27]

Fig. 9 (Case 3).—Postoperative roentgenogram of intracervical retrovascular anastomosis taken twenty-one days postoperatively.

Complications.—The only complication which occurred in our cases was a considerable dilatation and atony of the stomach which occurred in the first patient who had had both vagi severed. Dyspnea was caused and the patient was greatly troubled for a fortnight. Relief was obtained from repeated aspiration of the gastric contents. In both patients tachycardia was observed during the first postoperative days, disappearing on the third and fourth days, respectively. This symptom was ascribed to the severity of the operation rather than to stimulation of the cardiac nerves. No circulatory changes in the left upper extremity were noted. There were no pulmonary complications and the wounds healed by primary intention.

REPORT OF CASES OF INTRACERVICAL GASTROESOPHAGOSTOMY

CASE 3 (J. S.).—This patient was a 35-year-old woman who drank lye, by mistake, in 1937. After about two months her difficulty in swallowing required esophageal bouginage,

which she was later able to do to herself. One such performance, in 1947, was followed by a febrile reaction, accompanied by chest pains. After subsidence of the symptoms further decrease in the esophageal patency occurred so that, from that time, she only could swallow liquids although bouginage was repeated at regular intervals. On roentgen-ray examination it was seen that she had a constriction of esophagus starting at the sternoclavicular joint (Fig. 8).

Fig. 10 (Case 4).—Preoperative roentgenogram of high stenosis of the esophagus.

On Nov. 2, 1948, she was operated upon under endotracheal ether-oxygen anesthesia with curare. Intracervical esophagogastrostomy was carried out according to the method just described. As the esophagus showed fibrous changes, especially in the middle portion, it was feared that it could not be mobilized sufficiently to allow the stomach to be brought up into the neck unless the vagi were severed. The nerves were easily found on the lower third of the esophagus and were divided. The postoperative course was complicated by gastric atony and dilatation as noted previously. By November 27, she was cured and was

discharged in good condition. Follow-up examination on Aug. 7, 1949, showed that she had no difficulty in swallowing and had gained seven kilograms in weight. She was troubled with meteorism, and diarrhea alternating with constipation. The roentgen rays showed that the anastomosis was functioning well but that the atony and dilatation of the stomach had continued (Fig. 9).

CASE 4.—G. K. was a 24-year-old man who ingested lye by mistake six months prior to the writing of this paper. After subsidence of the first symptoms he began to have difficulties in swallowing which rapidly grew worse in spite of regular bouginage. He was only able to swallow semisolid food and lost thirteen kilograms in weight. He refused any further attempts at dilatation and requested operation. Roentgen rays showed evidence of stenosis apparently involving most of the thoracic esophagus (Fig. 10). On April 24, 1949, he was operated upon under intratracheal, ether-oxygen anesthesia, according to the method described previously. The anterior vagal trunk was preserved. Postoperative course was without complications and he was discharged on May 21, 1949, swallowing well. Roentgen rays showed the anastomosis to be functioning properly (Fig. 11).

Fig. 11 (Case 4).—Postoperative roentgenogram of intracervical retrovascular anastomosis taken fifteen days postoperatively.

SUMMARY

In corrosive stenoses of the thoracic esophagus patency can frequently be effected by surgical means. One may do an antethoracic plastic reconstruction, or an intrathoracic or intracervical anastomosis.

The antethoracic procedure has the disadvantages of the need for multiple stages to achieve the desired end result, and the uncertainty of the result being satisfactory. On the other hand the use of an intrathoracic, or intracervical, anastomosis makes possible the achievement of the desired result in one stage.

As in carcinoma of the esophagus, extent and location of the corrosive stricture must be considered separately. As far as the extent is concerned, it will only rarely be possible to resect the stenosed area and do an end-to-end anastomosis of the esophageal segments. In the great majority of cases the

re-establishment of the continuity of the digestive tract can only be accomplished by an anastomosis between the intact portion of the esophagus above the stricture and the stomach, which has been transplanted into the chest, or into the neck.

An esophagogastric anastomosis can be performed after a resection of the stenosed part of the esophagus and cardia, or without resection. The respective advantages and disadvantages of both methods are discussed.

As regards the location of the stricture the following approaches are considered from the technical point of view: (1) In stenoses of the lower fourth of the esophagus left thoracotomy is used. (2) In stenoses of the middle half either a left thoracotomy, particularly in strictures extending behind and above the arch of the aorta, or a right thoracotomy. (3) In stenoses of the upper fourth of the esophagus reconstruction of continuity is possible by high intracervical anastomosis after subtotal resection of the esophagus by the method of Sweet or of Garlock.

In two patients with stricture involving the middle half of the esophagus, palliative operation without resection of the esophagus was performed through a right thoracotomy approach after mobilization of the stomach through the abdomen.

In two other patients with stenosis of the entire thoracic esophagus; intracervical esophagogastrostomy without resection of the esophagus was performed by the retrovascular, intracervical route. This new operative method is described from the anatomical standpoint as well as from technical point of view.

Very good results were obtained in all four patients.

REFERENCES

1. Kleinschmidt, Otto: Die Eingriffe an der Brust und in der Brusthöhle. In Kirschner, M.: Operationslehre, Vol. 3, part 2, Berlin, 1940, Julius Springer.
2. Judin, S.: The Surgical Construction of Eighty Cases of Artificial Esophagus, Surg., Gynec. & Obst. **78**: 561-583, 1944.
3. Longmire, W. P., and Ravitch, M. M.: A New Method for Constructing an Artificial Esophagus, Ann. Surg. **123**: 819, 1946.
4. Stevenson, T. W.: Reconstruction of the Esophagus by a Skin-lined Tube, Surg. Gynec. & Obst. **84**: 197-202, 1947.
5. Rienhoff, W. F., Jr.: Antethoracal Transplantation of the Stomach in the Treatment of Congenital Atresia of the Thoracic Esophagus, Bull. Johns Hopkins Hosp. **82**: 496, 1948.
6. Bigger, I. A.: The Treatment of Congenital Atresia of the Esophagus With Tracheoesophageal Fistula, Ann. Surg. **129**: 588, 1949.
7. Taylor, H.: Further Report on the Operation of Oesophagectomy With Presternal Oesophagogastrostomy, Brit. J. Surg. **36**: 419, 1949.
8. Janeček, Z.: Antethoracal Reconstruction of the Esophagus, Rozhl. Chir. **24**: 413; 471, 1945.
9. Gross, R. E.: Treatment of Short Stricture of the Esophagus by Partial Esophagectomy and End-To-End Esophageal Reconstruction, Surgery **23**: 735, 1948.
10. Swenson, O., and Clatworthy, H. W.: Partial Esophagectomy With End-To-End Anastomosis in the Posterior Mediastinum, Bull. Am. Coll. Surgeons **32**: 235, 1947; Surgery **25**: 839, 1949.
11. Parker, E. F., and Brockington, W. S.: Esophageal Resection With End-To-End Anastomosis. Experimental and Clinical Observations, Ann. Surg. **129**: 588, 1949.
12. Sweet, R.: Subtotal Esophagectomy With High Intrathoracic Esophagogastric Anastomosis in the Treatment of Extensive Cicatricial Obliteration of the Esophagus, Surg. Gynec. & Obst. **83**: 417, 1946.

13. DeBakey, M. E., and Ochsner, A.: Subtotal Esophagectomy and Esophagogastrostomy for High Intrathoracic Esophageal Lesions, Surgery **23**: 935-951, 1948.
14. Clark, D. E., and Adams, W. E.: Transthoracic Esophagogastrostomy for Benign Strictures of the Lower Esophagus, Ann. Surg. **122**: 942, 1945.
15. Garlock, J. H.: Resection of Thoracic Esophagus for Carcinoma Located Above Arch of Aorta: Cervical Esophagogastrostomy, Surgery **24**: 1, 1948.
16. Mason, J. M.: The Surgical Treatment of Obstructive Lesions of the Esophagus, Ann. Surg. **127**: 1067, 1948.
17. Nissen, R.: Cervical Esophagogastrostomy Following Resection of Supra-aortic Carcinoma of the Esophagus, Ann. Surg. **130**: 21, 1949.
18. Allison, P. R.: Peptic Ulcer of the Oesophagus, J. THORACIC SURG. **15**: 308-317, 1946; Thorax **3**: 20, 1948.
19. Benedict, E. B.: New England J. Med. **224**: 408, 1941. Quoted by Brain, R. H.: Coincidental Strictures of Oesophagus and Stomach, Brit. J. Surg. **36**: 440, 1949.
20. Sweet, R.: A New Method of Restoring Continuity of the Alimentary Canal in Cases of Congenital Atresia of the Esophagus With Tracheoesophageal Fistula Treated by Immediate Primary Anastomosis, Ann. Surg. **127**: 757, 1948.
21. Rapant, V., and Kučera, J.: Oesophagojejunoanastomosis and Oesophagogastroanastomosis for Inoperable Carcinoma of the Esophagus and Cardia, Lékařské listy **3**: 397-402, 1948.
22. Rapant, V., and Zapletal, B.: Oesophagogastroanastomosis for Inoperable Carcinoma of the Middle Half of the Oesophagus, Rozhl. Chir. **28**: 183, 1949.
23. d'Allaines, and Dubost, C.: Communications sur la chirurgie de l'oesophage thoracique, Mém. Acad. de chir. **74**: 151, 1948; Arch. d. mal. de l'app. digestif. **37**: 425, 1948; J. de chir. **65**: 289, 1949.
24. Allison, P. R.: Oesophago-Jejunostomy for Irremovable Carcinoma of the Cardia, Thorax **1**: 239, 1946.
25. Macmanus, J. E.: Combined Left Abdominal and Right Thoracic Approach to Resection of Esophageal Neoplasms, Surgery **24**: 9-16, 1948.
26. Sweet, R. H.: Carcinoma of the Superior Mediastinal Segment of the Esophagus, Surgery **24**: 929, 1948.
27. Brittain, G. J. C.: Intravenous Procaine Hydrochloride; Postoperative Analgesia in 100 Cases, Anaesthesia **4**: 30-33, 1949.

AN ARTIFICIAL INTIMA FOR PERFUSION APPARATUSES

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IN SUCH a perfusion apparatus as the artificial heart the circulating blood is passing a number of glass and rubber tubes. The inside of these tubes is not as smooth as the intima of arteries or veins.

The perfusion of blood for some hours will therefore cause: (1) slight hemolysis, (2) some fibrin formation, and (3) tendency of foaming.

It has been shown that the fibrin formation and foaming can be avoided by using heavy doses of heparin. As much as 250 mg. of heparin per 1,000 ml. blood is needed for a three hours' perfusion. In intrathoracic operations, however, especially when a sternum splitting approach is used, this heavy heparin dose has been difficult to neutralize by protamine, resulting in a considerable risk of postoperative hemorrhage.

It has, therefore, been found of great value to produce an artificial intima for the circulating blood mainly to delay the clotting of blood. A smaller dose of heparin can then be used and at the end of the perfusion the surplus of heparin can more safely be neutralized by adding protamine to the blood.

In order to produce an artificial intima four different methods have been tried before the coating with Siloxan UHB 300 was chosen.

1. The water-repellent effect of paraffin wax was first tried to delay the clotting of blood in transfusion apparatuses. In the pump of the perfusion apparatus, however, where the rubber tubes are rhythmically constricted by compressed air, the paraffin was found to come off from the walls giving rise to embolism. Even though the blood was filtered before entering the artery of the perfused animal, the risk of embolism made it impossible to use the paraffin wax.

2. Polyvinylchloride has also been used for the coating of tubes. But when two surfaces coated with polyvinylchloride come into contact with each other, parts of the membrane tend to come off giving rise to embolism. The membrane of polyvinylchloride is not more adherent to the wall of the tubes than if a rift is produced, the blood may dissect away the membrane with the danger of embolism. For that reason the polyvinylchloride cannot be used as an artificial intima in the previously mentioned perfusion apparatus.

3. Recently certain plastics, the silicones, have been developed and found to possess water-repellent properties. Through the reaction of methylchlorosilane with the hydroxyl groups of adsorbed water on a surface, a very thin film of methylpolysiloxane is produced, resulting in a very low surface tension. Thus, a very high contact angle of that surface to liquid water is obtained. Water leaves the surface dry and stands in small droplets with a high contact angle.

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The same reaction is found to occur with cotton, wood, wool, silk, glass, rubber, and many other materials. Due to the humidity of the surrounding air, a film of water up to 100 molecules thick is found on the surface of glass which has stood at ordinary room conditions. The methylchlorosilanes appear to react with this strongly bound water film to liberate hydrogen chloride and attach methyl-bearing silicon atoms to the surface, thereby rendering the surface water repellent. The important point is that the silicon atoms appear to be chemically bound to the substrate, probably through oxygen. Once attached, the water-repellent film becomes a part of the object or the substance so treated and remains effective until abraded off (Rochow, 1947).

The organosilicon polymeric substances have a high thermal stability and insulating properties and are widely used in electric industry to produce a permanent water-repellent film maintaining a high surface resistance even when water has condensed on the surface. In 1946, Jaques and co-workers described the valuable properties in delaying the clotting of blood by one of these silicon compounds, General Electric Dri-Film No. 9987 (methyl-chlorosilane). The important point in the method of preparation was, however, to neutralize the liberated hydrochloric acid before the blood came in contact with the surface. The method described by Jaques and associates was, therefore, very time consuming and performed as follows:

All glassware and rubber tubes were carefully cleaned and dried before use.

1. Then methyl-chloro-silane (General Electric Dri-Film No. 9987) was applied in liquid form by pouring it into or through the glassware and rubber tubes used. The methyl-chloro-silane need only to come in contact with the object for a few seconds and the excess was poured off.

2. The object was then rinsed thoroughly with distilled water. The silicon is formed by hydrolysis and fixed to the material.

$$(CH_3)_3Si\,Cl + H_2O = (CH_3)_3Si\,OH + HCl$$

3. The hydrochloric acid liberated was removed by rinsing with very dilute ammonia water.

$$NH_4OH + HCl = NH_4Cl + H_2O$$

4. Then followed a copious washing with distilled water, and the articles were dried in hot air. This procedure gave a film much heavier than an unimolecular film. A fresh application of the silicon was made each time the glassware, etc., were used. The surface was improved with the second and third coatings. For aseptic use, the prepared objects were placed in boiling distilled water for two minutes.

We have used General Electric Dri-Film No. 9987 for preparation of a perfusion apparatus in brain perfusions in dogs. An effective water-repellent surface was obtained in the tubes. It was then possible to decrease the heparin doses to about 100 mg. heparin per 1,000 ml. blood, without clotting, fibrin formation, or foaming. One and one-half hours' brain perfusion did not cause any change of the blood due to the silicon. Nor was any change in the blood chlorides found, indicating that the washing had been carefully performed.

The rubber tubes which had been rhythmically constricted for three hours still had the same water-repellent surface. But the method was too time consuming for practical use, at any rate for a complicated perfusion apparatus.

In cooperation with the Uddeholm Company, Sweden, we have, therefore, worked out a method of coating tubes and glassware with silanoles without the roundabout way over methyl-chloro-silane. This simplification has made it possible to use the silicon as well in a more complicated perfusion apparatus with the same water-repellent effect.

By hydrolysis of methylethoxysilanes and condensation of these produces in appropriate molproportions siloxans are obtained as viscous liquids. This product is produced by the Uddeholm Company, Uddeholm, Sweden, under the registered trade-mark of Siloxan UHB 300.

METHOD

When the tubes and glassware are thoroughly cleaned and dried the Siloxan UHB 300 is poured through the tubes once. A contact with the object for a few seconds is enough. The objects are then kept in an autoclave at 120° C. for one hour. The tubes are placed in such a position that the surplus of Siloxan can run off. Afterward, it is necessary to wash all tubes with sterile saline solution before the perfusion of blood is performed. Thus, the remaining surplus of Siloxan is washed away at the same time as the condensation water in the tubes is removed. Otherwise this water will cause hemolysis. This preparation method has proved to be the best in coating a number of tubes in a more complicated perfusion apparatus. The machine can be coated when put together.

If an isolated part, as a syringe or needle, is coated, Siloxan is first forced through the object, which then is sterilized in an autoclave or boiled in distilled water for five minutes. After washing in saline solution the syringe is ready for use with blood.

This method of coating with Siloxan UHB 300 is now being used before all perfusion experiments. Extensive blood analyses have shown no change due to the Siloxan.

The advantages of the method:

Using Siloxan UHB 300, a water-repellent surface is obtained in glassware and tubes with the following result:

1. The friction is diminished.

2. The clotting is delayed, permitting a decrease of the heparin dose with 60 per cent. For three hours' circulation in the perfusion apparatus 100 mg. heparin per 1,000 ml. blood is sufficient. It has, therefore, been possible to use comparatively more protamine, 100 mg. (10 ml.) neutralizing 50 mg. heparin. The risk of hemorrhage in intrathoracic operations is then on the whole eliminated.

3. The fibrin formation is decreased.

4. The risk of foaming is diminished.

The artificial intima produced by Siloxan UHB 300 will, furthermore, render the apparatus easy to clean after use. After rhythmical constriction of the tubes for three hours, the walls are still as water repellent as after the coating. The same coating has been used for three different perfusions one week apart. At the mechanical cleaning of the apparatus, however, some part

may lose the water-repellent effect. It is, therefore, advisable to perform a new coating before each perfusion. We have also found it advantangeous to use Siloxan for coating of apparatuses for blood transfusions and intravenous administration, needles, cannulas, and syringes.

SUMMARY

A simple method is described for coating of glassware and rubber tubes with Siloxan UHB 300. An effective water-repellent surface is produced acting as an artificial intima diminishing the friction, the foaming, the fibrin formation, and delaying the clotting of blood so that a comparatively smaller heparin dose can be used.

REFERENCES

Bass, S. L., Hunter, M. J., and Kauppi, T. A.: Tr. Electrochemical Soc. **90**: 311, 1946.
Björk, V. O.: Acta chir. Scandinav. (Supp.) **4**: 137, 1948.
Björk, V. O.: Lancet **2**: 491, 1948.
Jaques, L. B., Fidlar, E., Feldsted, E. T., and Macdonald, A. G.: Canad. M. A. J. **55**: 26, 1946.
Jorpes, E., Edman, P., and Thaning, T.: Lancet **2**: 975, 1939.
Rochow, E. G.: Chemistry of the Silicones, New York, 1947.
Rochow, E. G.: Tr. Electrochemical Soc. **90**: 303, 1946.

COEXISTING BRONCHIOGENIC CARCINOMA AND COCCIDIOIDOMYCOSIS

Report of a Case

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EXPLORATORY thoracotomy in the management of suspicious intrathoracic lesions in which a positive diagnosis is not obtainable, although not universally accepted, is being performed with increasing frequency throughout the United States. It is only reasonable to expect that in our ambitious quest to conquer bronchiogenic carcinoma unusual lesions will be discovered at exploratory operations in increasing numbers. It has been recently pointed out by Brewer and Dolley that, in cases in which the lesion is found to be a benign one, the ideal treatment of most of these lesions is resection.

It has only been since the close of World War II that coccidioidomycosis has become a nationwide disease and must therefore be considered in the differential diagnosis of most chronic pulmonary lesions. As yet, the indications for surgical treatment of the pulmonary lesions of coccidioidomycosis have been limited, and reported series of cases have been few.

The following case is the first of its kind that we have seen. A search of the literature reveals that Churchill, in 1947, reported two cases of malignant lymphoma of the lung associated with coccidioidomycosis and stated that by personal communication Maier had reported a similar case. Other than these related cases our review of the literature has failed to reveal a reported case of primary bronchiogenic carcinoma associated with coccidioidomycosis in the same lung. Not having access to foreign and some American literature, except by title and published abstracts, our review is not complete and the author welcomes correction if a similar case has been reported.

CASE REPORT

J.W.B., a 53-year-old white male brush salesman, entered the hospital upon advice of a private physician. During a mass x-ray campaign in March, 1949, of the local tuberculosis association a 35-mm. photofluorographic film was made of his chest. Upon the basis of findings in the film he was recalled and given a tuberculin skin test which was negative. He was then advised to see a private physician for investigation of a suspicious lesion of the left chest. He neglected to report to a doctor until September, 1949. History revealed that the patient had had a chronic cough productive of one-fourth cup of thick yellow sputum for several years. In February, 1949, the patient contracted an upper respiratory infection characterized by marked aggravation of the cough and an increase in the amount of sputum to one cup per day. He did not consult a physician about the "cold" and symptoms spontaneously subsided after three months. Since that time, however, he had felt "run down" and fatigued and had not been able to work at his occupation more than two to three hours daily. He denied hemoptysis, night sweats, weight loss, and all other symptoms.

From the Surgical Service of the United States Naval Hospital.
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Past History.—The past history revealed that the patient had been subjected to the usual childhood diseases and influenza in 1918. He was diagnosed as having a peptic ulcer in 1935, which responded to a short period of rest and diet. He had intermittently consulted a physician for several years for "colitis" characterized by infrequent diarrhea and excessive mucus in the stools.

He had had mild hypertension (140/100) for four years prior to admission and for four years had been subject to typical anginal pain brought on by exertion and relieved by rest.

The patient was born in Illinois where he lived for 20 years, following which he moved to Florida where he resided for 15 years. For the five years preceding admission, he had lived in Southern California in Imperial Beach for two years and Chula Vista for three years. He had never been in the San Joaquin Valley. Neither had he been a resident of any of the southwestern states.

Family History.—The family history was noncontributory.

Physical Examination.—Physical examination revealed a well-nourished, well-developed, slightly obese, white man, who did not appear acutely or chronically ill. The blood pressure was 140/100, the pulse 88, and the respiration 22. The temperature was 99° F. Except for fine râles in the left lower lobe posteriorly which cleared on coughing, the physical examination was negative.

Laboratory studies showed a normal urine. The hemoglobin was 17 grams per 100 c.c. and the white cell count was 4,750 with normal differential distribution. Three examinations of the sputum for tubercle bacilli were negative. Tuberculin skin test in a dilution of 1:1000 produced a 20 by 20 mm. erythema. Serologic titer for coccidioidomycosis by complement fixation was not done preoperatively. Blood Kahn was negative. Electrocardiogram revealed marked showing of the interventricular conduction rate.

X-ray studies of the chest were done. Stereoscopic views of the chest revealed a peripheral mass lying against the lateral chest wall measuring 5 by 8 cm. The impression of the radiologist was (1) encapsulated fluid, (2) possible tumor of the lung or chest wall. Laminagraphs of this area were done which revealed the center of the mass to be at a depth of 12 cm. from the back and indicated that the mass was about 5 cm. in thickness. A diagnostic pneumothorax revealed the lung to be adherent to the chest wall at the site of the mass, and the radiologist was still unable to determine if the mass lay within the lung field. In addition, a 2-cm. circumscribed area of increased density was seen in the apex of the upper lobe, which, prior to the pneumothorax had occupied a position under the first rib and clavicle and was present in previous films in retrospect. Impression at this time was "tuberculosis, however, lung tumor cannot be ruled out."

Bronchoscopy revealed a small eroded area on the medial wall of the left main bronchus 1 cm. below the carina. Biopsy from this area was negative. Smears from aspirated material taken at bronchoscopy and repeated smears from sputum were studied by Papanicalaou's method were negative for evidence of malignancy. Bronchoscopy prior to surgery failed to reveal the previously described ulceration.

On Oct. 13, 1949, exploratory thoracotomy was performed. The left pleural cavity was opened through the sixth rib bed. There was a dense mass in the posterior apical segment of the upper lobe which was densely adherent to the chest wall. Closely adjacent to this in the apical portion of the lobe was a 2-cm. nodule which was very firm. There were pea-sized nodules distributed throughout the lower lobe. Upon freeing the mass from the chest wall, a 5 by 5 cm. thick-walled cavity filled with a caseous appearing material was entered. It was felt at that time that a tuberculous process had been encountered and a lobectomy was done. The vessels to the upper lobe and the superior pulmonary vein were triply ligated with silk ligatures and divided. The bronchus was severed and closed with simple interrupted sutures of fine silk. The chest wall was closed in individual layers with interrupted cotton sutures. Intercostal tubes were placed in the fourth interspace in the anterior axillary line and in the ninth interspace in the posterior axillary line and connected to a water-seal bottle.

Frozen section of the removed specimen during the operative procedure was reported as epidermoid carcinoma. This section was taken from the solid tumor mass, the pathologist assuming that the cavitation was necrotic tumor. On the basis of the report it was deemed that the lesion was inoperable because of the chest wall invasion over a wide area. Also at the time the report was received, the operating time had exceeded three and one-half hours and the condition of the patient would not have permitted further resection.

Fig. 1.—The formalin fixed upper lobe showing the relation of the two lesions. The rounded discrete mass lying superiorly is the epidermoid carcinoma. The larger mass with cavitation is the lesion found to contain *Coccidioides imitis*.

The patient's convalescence was uneventful, and the tubes were removed on the third postoperative day.

Pathologic Report.—Gross examination of the specimen revealed it to consist of the left upper lobe of the lung measuring 16 by 9 by 6 cm. The pleural surface was roughened on its lateral aspect. The lung on palpation revealed two distinct tumors, one located near the periphery in the mid-portion of the lung, and the other located superiorly to and deeper in the lung parenchyma than previously described. Accompanying the specimen were two lymph nodes which were peribronchial nodes of the left upper lobe. The nodes appeared to be grossly involved with neoplastic tissue. On sectioning the lung a firm tumor mass 2 cm. in diameter was located in the apical segment of the lobe. This mass was grayish-white, discrete, but not encapsulated. A second mass lying lateral and inferior to the first mass was found to measure 5 cm. in all diameters. The mass was filled with white, cheesy tissue, and the wall of the mass was granulatory in character. It was encapsulated and no tumor was seen grossly. The remainder of the lung parenchyma was not remarkable.

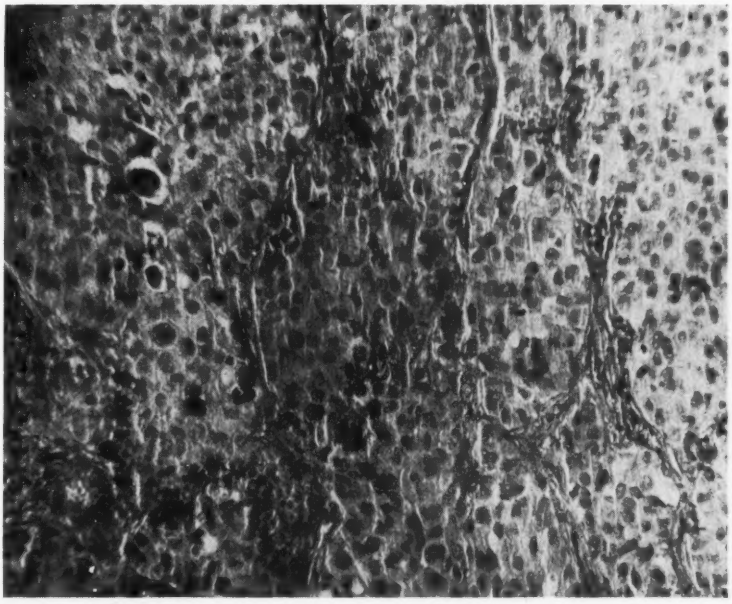

Fig. 2.—Photomicrograph of a section from the carcinoma which is a squamous-cell or epidermoid carcinoma.

Microscopic examination of the lymph node revealed sheets of anaplastic epidermoid cells completely replacing the normal architecture.

Sections from the solid tumor mass from the lung revealed an anaplastic epidermoid carcinoma with many mitoses, hyperchromatic bizarre nuclear patterns, and complete loss of tissue architecture. A segment of bronchiolar epithelium revealed a marked epidermidization of the lining epithelium.

Sections of the peripheral mass showed it to consist of a rather dense fibrous wall lined by necrotizing granulation tissue. The center of the mass was composed of necrotic tissue. Double-contoured spherical spores measuring from ten to fifty micra, characteristic of *Coccidioides immitis,* were found distributed in the necrotic tissue and in the wall of the lesion.

The diagnosis was: (1) Epidermoid carcinoma of lung with metastasis to regional lymph nodes. (2) Coccidioidomycosis of the lung.

After pathologic examination had been complete it was apparent that two separate lesions were present and that the carcinoma was localized and was grossly operable. Complete mediastinal lymph node resection had not been done at the time of surgery. It was decided, therefore, that reoperation with complete pneumonectomy and excision of lymph nodes was indicated.

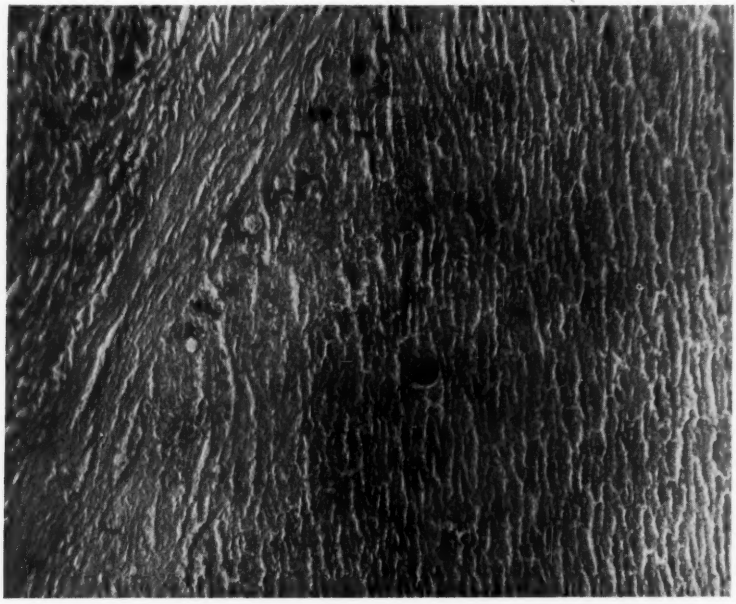

Fig. 3.—Photomicrograph of the cavitary lesion. The section is through the wall of the lesion. Three spores of *C. imitis* are clearly visible in this section.

On Oct. 31, 1949, the patient was operated upon again. The previous incision was reopened. The left lower lobe was mobilized. The pericardium was opened and the common left pulmonary vein was triply ligated with heavy silk and divided. The pulmonary artery was mobilized to its origin and similarly ligated. The left main bronchus was amputated within one centimeter of the carina and closed with simple interrupted sutures of 0 silk. All accessible hilar and mediastinal lymph nodes were resected. No evidence of tumor was seen grossly in the specimens. The pleural cavity was closed, and the chest wall was repaired as before. Pathologic examination of the removed tissue revealed no evidence of carcinoma. All lymph nodes were negative. A small 1 by 1 cm. area of granulomatous tissue was found in the pulmonary ligament which proved to be a pleural lesion of coccidioidomycosis.

The patient's postoperative course was uneventful until the fourth postoperative day, when he suddenly began coughing up blood-stained material and rapidly went into profound circulatory collapse. Examination revealed a tension pneumothorax on the operated side with a marked shift of the mediastinum to the right. It was apparent that a broncho-pleural fistula had developed. An intercostal tube was inserted by trochar and connected to a water-seal bottle. Intratracheal aspiration was repeatedly done and bronchoscopy was employed to remove material aspirated from the pleural cavity through the opened

bronchial stump. Evidence of a rather marked paradoxical mediastinal motion was present and pulmonary edema developed in the right lung. The patient was digitalized with slight improvement. The patient's course from this point was progressively downhill, and he expired from cardiac failure on the seventh postoperative day.

Autopsy revealed besides the disrupted bronchial stump and an early empyema that the right lung was extremely emphysematous. Also a grade 4 coronary arteriosclerosis was present. There were small nodules in the right lung which proved to be focal lesions of coccidioidomycosis. No evidence of residual or metastatic carcinoma could be detected.

A diagnosis of active coccidioidomycosis could have been made by employing complement fixation tests; however, if it had been made preoperatively the carcinoma would have been neglected until a much later date.

Although the operative procedure was performed because carcinoma could not be ruled out, we feel that the tumor in this case was an incidental finding. Whether pneumonectomy was indicated in this case remains a question. The author feels that since metastatic tumor was found in the peribronchial lymph nodes at the first operation, reoperation was imperative.

REFERENCES

1. Churchill, E. D.: Malignant Lymphoma of Lung and Pulmonary Coccidioidomycosis; Clinic on Surgical Lesions of Lung With Consolidation, S. Clin. North America **27**: 1113-1120, 1947.
2. Brewer, L. A., III, Jones, W. M. G., and Dolley, F. S.: Nonmalignant Intrathoracic Lesions Simulating Bronchiogenic Carcinoma, J. THORACIC SURG. **17**: 439-463, 1948.

RESPIRATORY AND CIRCULATORY STUDIES AFTER PNEUMONECTOMY IN CHILDHOOD

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ALTHOUGH seventeen years have elapsed since the first successful one-stage pneumonectomy was performed, relatively little detailed information is available regarding respiratory and circulatory function of individuals in whom a lung has been removed. This dearth of knowledge is particularly striking in pneumonectomized children.

In 1937, Bremer[1] investigated the histologic changes in the remaining lung occurring after experimental pneumonectomy. In growing cats what was considered to be a true hyperplasia of the parenchyma was found, whereas in adult animals simple alveolar distention took place.

Longacre, Carter, and Quill[2] determined lung volume, response to exercise, and tolerance to low oxygen in two groups of dogs following pneumonectomy. The adult animals showed marked deficiency in respiratory reserve. Although their functional residual air volumes were abnormally large to such extent that they equalled prepneumonectomy values, they could perform moderate exercise adequately. Operated puppies, on the other hand, did as well as their unoperated litter mates on both moderate and strenuous effort even though the remaining lung filled the entire thorax.

In a later communication Longacre and Johansmann[3] reported experimental studies four years after pneumonectomy which represents about one-half the life span of the normal dog. In the adult animals fragmentation of alveoli and loss of elastic tissue were found, while the dogs operated on as puppies demonstrated only a slight amount of alveolar membrane rupture. The physiologic performance of the latter group was nearly normal whereas the former showed deficiencies on all tests.

There have been a number of investigations on adult human beings following pneumonectomy but only two on children, reported by Lester and associates.[4a] Three children aged 9, 12, and 14 years who had left pneumonectomies were studied. All three cases were complicated by postoperative empyema. When the study was made, one to three years after operation, all were in good clinical condition. They performed exhausting exercise without changes in blood gas composition other than those expected in normal individuals. The lung volumes were larger than expected for one normal lung but not as large as predicted for two. In none of them did the lung fill the opposite hemithorax completely. The

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patient with the most marked herniation had poorer function than the other two. The authors concluded that overdistention of the lung following pneumonectomy was undesirable and that steps should be taken to prevent displacement of the mediastinum.

In a second paper[4b] the same three patients were studied five to six and one-half years after operation in addition to a 20-year-old girl who had a left pneumonectomy completed at the age of 16 years. Two patients showed improved adaptation and good performance. The remaining two showed a drop in arterial oxygen saturation after exhausting exercise. The latter cases also had reduced breathing reserve and increased ratio of residual air to total capacity. In one of these cases, the 20-year-old girl, a thoracoplasty had been performed in an attempt to relieve distention with some subjective but no objective improvement.

The preceding studies include only patients with postoperative empyema in whom the mediastinum may be more rigid than normally is the case. One of the patients was 16 years old at the time of operation and therefore past her maximal growth period. It seemed, therefore, desirable to us to study a larger series of children on whom pneumonectomy uncomplicated by empyema had been performed in early childhood.

CLINICAL MATERIAL

Of the twenty-two children who have had a pneumonectomy at Barnes Hospital, ten have been studied. Of the remaining twelve, five died in the immediate postoperative period, one survived eight years but met an accidental death, two were too young for satisfactory evaluation, and four cannot be located.

In the group examined, operation was performed because of unilateral bronchiectasis or abscess in seven and actinomycosis, granuloma of unknown etiology, and lipoid pneumonia in the remainder. In all but one of these cases there is no disease in the remaining lung. The group includes seven girls and three boys whose ages at operation ranged from 3 to 14 years. At the time of study eight months to thirteen years had elapsed since operation which was performed on the right in four and on the left in six. There was only one postoperative empyema and no bronchopleural fistulas. All but three pneumonectomies were done by individual ligation technique.

At the time of study all but the patient with residual disease were leading normal lives. One girl (J. W.) now 21 years old is a champion gymnast and a 19-year-old boy (S. H.) is doing construction work 4,000 to 5,000 feet above sea level. None of the patients had any significant scoliosis or other cosmetic deformity. Age at operation, sex, height, weight, body surface, and diagnosis are given in Table I.

METHODS

The patients were examined early in the morning, fasting or after a light breakfast. Vital capacity and its subdivisions were determined in the supine position with a standard metabolism machine filled with oxygen. The complemental air values include tidal air

as suggested by Christie. A wait of at least twenty minutes was allowed after these tests in order to restore normal gas relationships in the lung. Residual air was then measured with the patient supine by the closed method of Cournand and associates,[5] modified by placing an additional three-way valve between the main three-way valve and the spirometer circuit. This renders it unnecessary for the patient to hold his breath at the end of the alveolar sampling. The technique involved seven minutes of oxygen breathing during which time the expired air was collected in a spirometer. At the end of seven minutes an alveolar sample was obtained. The nitrogen percentage of this and of the spirometer content was determined in the Van Slyke-Neill apparatus according to the method described by Peters and Van Slyke[6] with minor modifications. Duplicate determinations checked within .03 volumes per cent.

Considerable difficulty was encountered in residual air determinations on young children and the results cannot be expected to check as well as in adults. However, alveolar nitrogen values in duplicate tests checked adequately in all instances. The difference between duplicate values of the residual air determinations was less than 12 per cent in five subjects. In the remaining five it varied from 16 to 34 per cent. Only in patients with large residual air compartments were the differences between duplicate determinations great.

To measure maximum breathing capacity, the patient was encouraged to breathe as deeply and as rapidly as possible in the erect position for two periods of fifteen seconds and two periods of thirty seconds. The expired air was collected in a 350-liter spirometer by means of two one-way flutter valves. The diameter of the connecting tubing was one and one-half inches. The highest value of the four obtained, expressed as liters per minute, corrected to prevailing barometric pressure at 37° C., and saturated with water vapor, was used.

Following another twenty-minute rest period a femoral arterial blood sample was withdrawn in a lightly lubricated syringe the dead space of which was filled with undiluted heparin. The patient then performed a standard exercise which consisted of walking on a treadmill at a five degree grade for seven minutes at a speed of either 2.5 or 3.2 miles per hour, depending on the size of the subject. During each minute of exercise and at three, five, and ten minute intervals afterward pulse and respiratory rates were recorded. Immediately upon completion of exercise another arterial blood sample was withdrawn. Part of each blood sample was centrifuged under oil and the plasma collected over mercury for carbon dioxide content and pH determinations in duplicate. The former was done according to the 0.2 c.c. method as described by Peters and Van Slyke,[6] the latter with the method of Hastings and Sendroy[7] using bicolor standards. The remaining blood was used for the determination in duplicate of oxygen content and capacity in the Van Slyke-Neill apparatus. All gasometric analyses checked within 0.12 volumes per cent. The carbon dioxide tension was computed from the pH and carbon dioxide content by means of the Henderson-Hasselbalch equation using the line chart of Peters and Van Slyke.[6]

Finally, inspiratory and expiratory posterior-anterior x-ray films of the chest were taken as well as a lateral film of the nonoperated side in most instances. These were reviewed by Dr. William B. Seaman of the Mallinckrodt Institute of Radiology who rated each case from one to four plus for diaphragmatic motion, mediastinal motion, and degree of herniation of the lung into the opposite hemithorax. An estimate was also made of the size of the thoracic cage on the operated side expressed as a percentage of the size of the nonoperated side in the inspiratory position.

RESULTS

The results of these studies are shown in Tables I to VI. The patients listed above the rule are children with the left lung remaining, those below, the right. G. K. will be discussed separately since she was the only child in whom there was residual disease.

TABLE I. BODY CHARACTERISTICS AND DIAGNOSES OF CASES STUDIED

SUBJECT	SEX	HEIGHT IN CM.	WEIGHT IN KG.	SURFACE AREA IN M^2	AGE AT OPERATION (YEARS)	NUMBER OF YEARS SINCE OPERATION	DIAGNOSIS
Left Lung Remaining							
M.P.*	F	167.8	51.8	1.57	3	12	Infected cystic disease
J.L.*	M	179.0	54.5	1.68	12	4	Chronic lung abscess with bronchopleural fistula
D.T.	F	165.0	61.7	1.67	14	3	Actinomycosis
G.K.†	F	147.3	42.2	1.30	10	1	Granuloma of lung
Right Lung Remaining							
J.R.*	M	127.5	26.8	0.97	5	2	Lung abscess with bronchiectasis
J.B.‡	F	140.0	31.8	1.12	6	6	Bronchiectasis due to aspirated foreign body
G.S.	F	144.0	34.0	1.05	12	8/12	Granuloma of unknown etiology
B.S.	F	151.0	37.2	1.26	3	10	Bronchiectasis due to aspirated foreign body
S.H.	M	184.0	68.1	1.88	13	6	Bronchiectasis due to aspirated foreign body
J.W.	F	162.5	55.9	1.58	8	13	Bronchiectasis due to aspirated foreign body

*Preoperative empyema.
†Residual disease in remaining lung.
‡Postoperative empyema but no bronchopleural fistula.

The oxygen saturation before and after exercise (Table II) was within normal range in all subjects, increasing 1 to 4 per cent in all but M. P. after effort. An oxygen capacity rise averaging 0.73 volumes per cent similar to that found in normal subjects was also noted. The plasma carbon dioxide content and pH were within the normal range before and after exercise as was the carbon dioxide tension except in the case of G. S. This last value is undoubtedly due to a technical error. The respiratory rates with exercise (Table III) were higher than the normal figures given by Robinson.[9] At the end of

TABLE II. ARTERIAL BLOOD STUDIES BEFORE AND AFTER EXERCISE

	OXYGEN SATURATION %		OXYGEN CAPACITY VOL. %		PLASMA CO_2 CONTENT MEQ./L		PLASMA PH		ARTERIAL CO_2 TENSION MM. HG	
SUBJECT	BEFORE EXERCISE	AFTER EXERCISE	BEFORE EXERCISE	AFTER EXERCISE	BEFORE EXERCISE	AFTER EXERCISE	BEFORE EXERCISE	AFTER EXERCISE	BEFORE EXERCISE	AFTER EXERCISE
Left Lung Remaining										
M.P.	95.38	95.10	17.39	18.28	24.30	18.75	7.50	7.35	32.9	36.1
J.L.	95.56	96.87	20.26	21.12	24.44	22.38	7.47	7.47	35.0	32.3
D.T.	96.00	96.97	17.75	19.16	24.54	19.45	7.50	7.40	33.0	33.0
G.K.*	90.18	81.32	22.01	22.99	26.20	24.10	7.50	7.35	35.0	46.0
Right Lung Remaining										
J.R.	93.98		17.95		22.42		7.40		35.7	
J.B.	94.60	95.35	18.43	18.97	24.63	24.11	7.47	7.47	35.2	35.0
G.S.	95.28	99.25	18.65	19.41	22.42	25.78†	7.43	7.38	35.2	51.9
B.S.	96.83	97.83	16.63	16.63	20.77	20.45	7.45	7.40	31.0	35.1
S.H.	97.08	99.68	22.60	23.07	24.42	23.98	7.55	7.50	29.3	32.0
J.W.	94.00	96.52	17.35	18.26	18.85	22.02	7.35	7.37	35.8	39.1

*Residual disease in remaining lung.
†Probable technical error.

TABLE III. PULSE AND RESPIRATORY RATES DURING AND AFTER EXERCISE

SUBJECT	PULSE		RESPIRATIONS	
	MAXIMUM RATE WITH EXERCISE	RATE 10 MINUTES AFTER EXERCISE	MAXIMUM RATE WITH EXERCISE	RATE 10 MINUTES AFTER EXERCISE
	Left Lung Remaining			
M.P.	148	102	32	20
J.L.	136	60	32	20
D.T.	192	92	44	20
G.K.*	140	124	84	42
	Right Lung Remaining			
J.R.	112	96	40	22
J.B.	132	92	40	20
G.S.	156	118	30	20
B.S.	176	104	36	16
S.H.	140	76	28	17
J.W.	148	84	36	16

*Residual disease in remaining lung—tolerated only two minutes of exercise.

a ten-minute recovery period, however, the rate was 22 or below in all subjects. The pulse rate in the same interval had returned to 100 or below except in one individual studied only eight months after operation. Those in better physical condition such as S. H., J. W., and J. L. had the slowest pulse at the end of the ten-minute rest period.

Table IV lists the absolute values found for each of the subdivisions of the lung volume, the maximum breathing capacity, and the per cent of alveolar nitrogen after seven minutes of oxygen breathing. To evaluate these results some standard of reference is necessary. The values for comparable normals reported in the literature by different investigators vary considerably. The prediction formulas of Baldwin and associates for vital capacity and maximum breathing capacity[8] are satisfactory in older children and adults but are not derived from or useful for predicting values in younger children. Thus figures obtained by using these formulas are much larger than those found by Robinson[9] in normal boys and by Wilson and Edwards[10] in children of both sexes.

TABLE IV. TOTAL LUNG VOLUME—ITS SUBDIVISIONS AND MAXIMUM BREATHING CAPACITY*

SUBJECT	TIDAL VOLUME (C.C.)	COMPLEMENTAL VOLUME (C.C.)	RESERVE VOLUME (C.C.)	VITAL CAPACITY (C.C.)	RESIDUAL VOLUME (C.C.)	TOTAL VOLUME (C.C.)	$\frac{\text{RESIDUAL}}{\text{TOTAL}} \times 100$	% ALVEOLAR N_2 AFTER 7 MIN. O_2 BREATHING	MAXIMUM BREATHING CAPACITY (L/MIN.)
				Left Lung Remaining					
M.P.	313	1585	501	2035	3271	5357	61.0	6.41	45.3
J.L.	628	1909	602	2510	1124	3635	30.8	1.05	63.5
D.T.	289	1417	210	1680	650	2277	28.6	1.27	48.9
G.K.†	236	483	129	559	747	1359	54.6	1.86	30.9
				Right Lung Remaining					
J.R.		1063	330	1118					46.0
J.B.	319	904	186	1116	1038	2128	48.8	1.32	35.2
G.S.	369	1055	190	1212	2706	3900	69.1	3.86	36.4
B.S.	310	1500	310	1810	1060	2870	37.0	1.08	54.1
S.H.	536	2678	1102	3640	1241	5025	24.7	1.90	92.5
J.W.	479	1915	718	2660	997	3625	27.4	1.45	52.0

*All volumes are at barometric pressure 37° C. and saturated with water vapor.
†Residual disease in remaining lung.

TABLE V. COMPARISON OF VITAL CAPACITY, TOTAL CAPACITY, AND MAXIMUM BREATHING CAPACITY EXPRESSED IN PER CENT OF VARIOUS STANDARDS FOR TWO NORMAL LUNGS

SUBJECT	AGE AT STUDY (YEARS)	SEX	VITAL CAPACITY*					TOTAL CAPACITY*				MAXIMUM BREATHING* CAPACITY	
			I	II	III	IV	V	I	II	III	IV	I	II
Left Lung Remaining (Normal—45 per cent of total)													
M.P.	15	F	54	60	55	75	71	113	127	114	121	41	45
J.L.	16	M	54		51	52		63		58	57	51	61
D.T.	17	F	51		45	53		55		49	51	46	
G.K.†	10	F	18	30	19		23		57	36		36	39
Right Lung Remaining (Normal—55 per cent of total)													
J.R.	7	M	33		65		61						
J.B.	12	F	39	59	51		54		90	76		48	52
G.S.	12	F	41	64	55		63		165	140		53	46
B.S.	13	F	57	87	61		79		110	77		66	70
S.H.	19	M	77		73	76		85		77	82	64	
J.W.	21	F	84		72	85		91		78	82	54	

*I. Formulas of Baldwin and associates.[8]
II. Normal values Cournand and associates.[4]
III. Normal values Robinson.[9]
IV. Normal values Hurtado and associates.[11, 12]
V. Normal values Wilson and Edwards.[10]
†Residual disease in remaining lung.

In the only study of normal female subjects (Hurtado and associates[11]) the age range is from 17 to 34 years. The difficulty in comparing our results with normal data is evident in Table V where the values obtained in our subjects are expressed as a percentage of those predicted for two lungs by various authors for normal subjects of similar age and body fluid. As an example, it can be seen that the vital capacity of B. S. ranged from 57 to 79 per cent of normal with different standards.

In all cases the tidal air was greater than would be expected for one lung; and in most, subjects approached the normal value for an intact individual. Complemental air was also greater than predicted. Reserve air was larger than expected for one lung in four; in the remaining six it was less. All of

TABLE VI. RADIOLOGIC EVALUATION OF DIAPHRAGMATIC AND MEDIASTINAL MOTION AND SIZE OF OPERATED HEMITHORAX*

SUBJECT	DEGREE OF DIAPHRAGMATIC MOTION	DEGREE OF MEDIASTINAL MOTION	DEGREE OF HERNIATION INTO THE OPPOSITE HEMITHORAX	OPERATED SIDE AS PER CENT OF THE NONOPERATED
Left Lung Remaining				
M.P.	2	0	4	80
J.L.	4	1	3	70
D.T.	4	1	1	70
G.K.†	2	1	3	100
Right Lung Remaining				
J.R.	1	2	2	90
J.B.	2	1	1	40
G.S.	1	0	1	100
B.S.	2	1	4	90
S.H.	3	4	2	100
J.W.	4	4	4	90

*Magnitude of motion rated from 1 to 4 plus.
†Residual disease in remaining lung.

our cases had vital capacity values at least as great as could be predicted for the remaining lung. In some it was markedly greater. The maximum breathing capacity similarly showed values as large as, or up to 10 per cent greater than, that predicted for one lung. As the resistance in our system was higher than in the apparatus used in the control studies with which we are making comparison, the performance on this test might be better than the percentages would indicate.

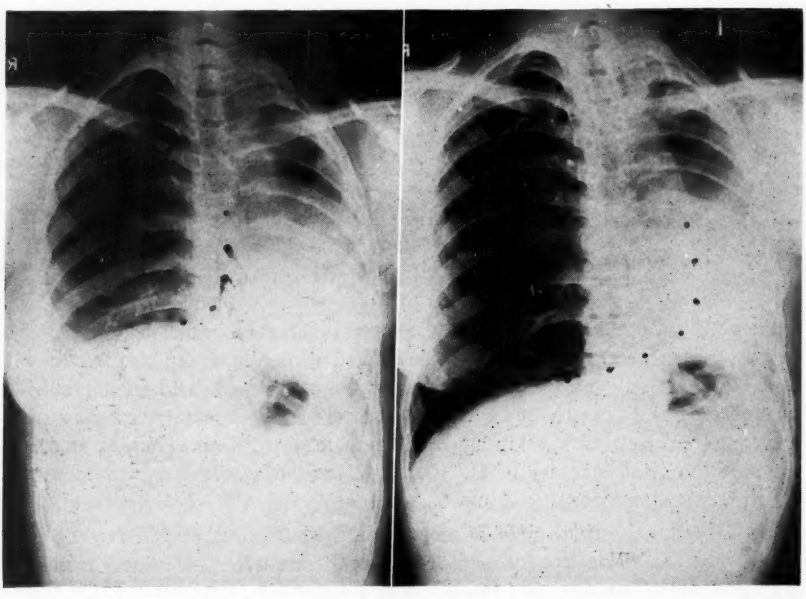

Fig. 1 (J. W.).—Expiratory (left) and inspiratory (right) roentgenograms taken thirteen years after left pneumonectomy. Moderate mediastinal shift and marked herniation of remaining lung into opposite hemithorax. Wide range of mediastinal motion (dotted lines) and diaphragmatic descent (two interspaces) associated with superior physical capacity and normal ratio of residual air to total lung volume (27 per cent).

Evidence of an increase in size of the remaining lung is afforded by values of total lung volume greater in all cases studied than that predicted for a similar normal lung. In three individuals (M. P.,* G. S., and B. S.) the total capacity was even greater than expected in a normal individual with two functioning lungs. In two of these children (M. P. and G. S.) emphysema is suggested by the very high ratio of residual air to total capacity. In the third subject (B. S.) as well as in three others (J. L., J. W., and S. H.) increased total capacity went pari passu with larger than expected vital capacity and in them a hyperplasia of lung tissue may have occurred.

In the two patients with highest residual air volumes high alveolar nitrogen values were encountered after seven minutes of oxygen breathing. Duplicate

*At the time of her operation 12 years ago, so far as was known, she was the first very young child (3 years of age) to have a pneumonectomy. There was some worry that the procedure might interfere with her normal growth and development, but fortunately she appears and acts now like any normal girl of 15 years.

determinations of these nitrogen concentrations in alveolar air checked satisfactorily. These high values are believed to be evidence of poor ventilation of some portions of the lung and not due to technical errors. In all other patients the alveolar nitrogen concentrations were within normal limits. Of the eight on whom satisfactory values were obtained, four had a ratio of residual air to total capacity below 30 per cent which may be taken as normal for this age group. The other four all had ratios which must be considered above normal.

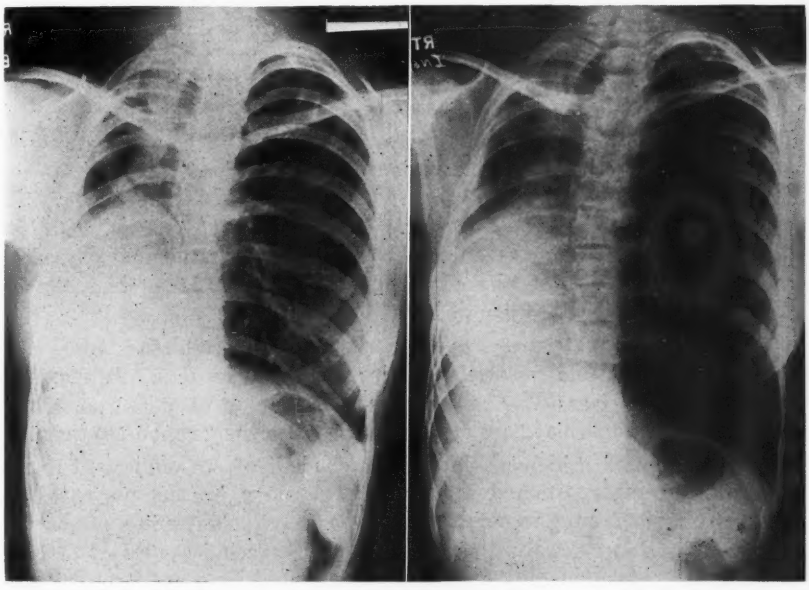

Fig. 2 (M. P.).—Expiratory (left) and inspiratory (right) roentgenograms taken twelve years after right pneumonectomy. Marked herniation of lung and marked mediastinal shift with heart in right thorax. Only moderate diaphragmatic motion (one interspace) and no mediastinal motion on deep inspiration. Residual air compartment 69 per cent of total lung volume.

The condition of the remaining lung, as judged from the x-ray films, correlated well with the functional studies. All patients had herniation of the lung into the opposite hemithorax to a greater or less degree. However, in those patients with evidence of a wide range of mediastinal and diaphragmatic motion the herniation, although large, did not result in a large residual air compartment, and their ventilatory performance was excellent (Fig. 1). As the diaphragmatic and mediastinal mobility was reduced the herniation took place in association with increased residual air. In the two cases with the highest ratio of residual air to total capacity, no mediastinal motion was found (Fig. 2). In other words, the highest residual air percentages were all associated with two plus or less motion of both mediastinum and diaphragm. The two subjects with the largest vital capacities as compared to the predicted values had the greatest mediastinal and diaphragmatic movement.

In six of the ten, the size of the hemithorax on the operated side, as judged by radiography, was essentially the same as that on the unoperated side. The postoperative empyema in J. B. may have resulted in a contraction of ipsilateral hemithorax to 40 per cent of the size of the opposite side. The remaining three patients had slightly reduced ipsilateral hemithoraces; two of these experienced empyema before operation but the other had no pre- or postoperative complications.

Thus far G. K. has not been discussed because of the disease in her remaining lung. She is a pulmonary cripple, and could exercise for only two minutes at the end of which time her arterial oxygen saturation had fallen to 81 per cent and carbon dioxide tension had risen to 46 mm. Hg. Her vital capacity and maximum breathing capacity were less than expected for the remaining lung and her residual air compartment was large. She is the only patient who manifested any abnormalities in blood gas values on exercise.

SUMMARY AND CONCLUSIONS

There is no apparent correlation between age at operation and physiologic performance as determined by the methods used. Except for perhaps the first year, the interval after operation would seem not to influence the result.

In comparing our patients with Cournand's four children studied after pneumonectomy, we find essentially similar vital capacity data. In maximum breathing capacity two of his subjects exceeded the best of our series, but the difference in technique may have made this discrepancy more apparent than real.

We have found a high residual air in one-half of our subjects, but even this finding, together with reduced ventilatory ability, has not prevented any of them from performing moderate exercise for seven minutes in a normal way and without fall in arterial oxygen saturation. Cournand has raised the question whether herniation of the remaining lung into the opposite hemithorax should not be prevented by thoracoplasty or oleothorax. We find, however, that herniation of considerable degree can be associated with low residual air values and excellent vital capacity and maximum breathing capacity if the mobility of diaphragm and mediastinum is maintained at a maximum. One of the most striking and provocative findings from our studies is that the best performance on all tests was found in the two most active patients, the gymnast and the construction worker, each of whom has made a concerted effort to overcome his handicap. This observation suggests the importance of physical training after pneumonectomy and the maintenance of the maximum mobility of diaphragm and mediastinum.

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REFERENCES

1. Bremer, J. L.: The Fate of the Remaining Lung Tissue After Lobectomy or Pneumonectomy, J. THORACIC SURG. 6: 336, 1937.
2 (a) Longacre, J. J., Carter, B. N., and Quill, L. McG.: An Experimental Study of Some of the Physiological Changes Following Total Pneumonectomy, J. THORACIC SURG. 6: 237, 1937.

(b) Carter, B. N., Longacre, J. J., and Quill, L. McG.: A Study of the Changes in Cardiorespiratory Physiology Following Total Pneumonectomy in Young Developing Animals, J. THORACIC SURG. **7**: 326, 1938.

3. Longacre, J. J., and Johansmann, R.: An Experimental Study of the Fate of the Remaining Lung Following Total Pneumonectomy, J. THORACIC SURG. **10**: 131, 1940.

4 (a) Lester, C. W., Cournand, A., and Riley, R. L.: Pulmonary Function After Pneumonectomy in Children, J. THORACIC SURG. **11**: 529, 1942.

(b) Cournand, A., Himmelstein, A., Riley, R. L., and Lester, C. W.: A Follow-Up Study of the Cardiopulmonary Function in Four Young Individuals After Pneumonectomy, J. THORACIC SURG. **16**: 30, 1947.

5. Cournand, A., Baldwin, E. deF., Darling, R. C., and Richards, D. W., Jr.: Studies on Intrapulmonary Mixtures of Gases. IV. The Significance of the Pulmonary Emptying Rate and a Simplified Open Circuit Measurement of Residual Air, J. Clin. Investigation **20**: 681, 1941.

6. Peters, J. P., and Van Slyke, D. D.: Quantitative Clinical Chemistry, Vol. II (Methods), Baltimore, Williams & Wilkins Company.

7. Hastings, A. B., and Sendroy, J., Jr.: The Colorimetric Determination of Blood pH at Body Temperature Without Buffer Standards, J. Biol. Chem. **61**: 695, 1924.

8. Baldwin, E. deF., Cournand, A., and Richards, D. W., Jr.: Pulmonary Insufficiency. I. Physiological Classification, Clinical Methods of Analysis, Standard Values in Normal Subjects, Medicine **27**: 243, 1948.

9. Robinson, Sid: Experimental Studies of Physical Fitness in Relation to Age, Arbeitsphysiologie **10**: 3, 1938.

10. Wilson, M. G., and Edwards, D. J.: The Vital Capacity of the Lungs and Its Relation to Exercise Tolerance in Children With Heart Disease, Am. J. Dis. Child. **22**: 443, 1921.

11. Hurtado, A., Fray, W. W., Kaltreider, N. L., and Brooks, W. D. W.: Studies of Total Pulmonary Capacity and Its Subdivisions. V. Normal Values in Female Subjects, J. Clin. Investigation **13**: 169, 1934.

12. Hurtado, A., and Boller, C.: Studies of Total Pulmonary Capacity and Its Subdivisions. I. Normal, Absolute and Relative Values, J. Clin. Investigation **12**: 793, 1933.

PERICARDIAL CELOMIC CYSTS AND PERICARDIAL DIVERTICULA

A Concept of Etiology and Report of Cases

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THIN-WALLED cysts of the mediastinum, filled with a clear fluid and lined with mesothelium, constitute a relatively new clinicopathologic entity. The contemporary problem of the origin and significance of these cysts may be said to have arisen in 1934, when Pickhardt[1] first reported the successful removal of a "pleuropericardial cyst" from the mediastinum. Prior to this time, discussion of the etiology of these cysts had been confined to pathologico-anatomic reports which date well back into the past century. Rokitansky[2] in 1854, Cruveilhier[3] in 1849, Hird[4] in 1848, Coën[5] in 1885, and Rohn[6] in 1905, described cysts which they considered to have been formed by herniation of the serosa of the pericardium through the fibrous leaf of the pericardium, or "pulsion diverticula." Rohn[6] and Atayas-Maraty,[7] in 1885, described cystic lesions which they explained as having been formed by the pinching off of a serosal hernia of the pericardium. Grabowski,[8] in 1926, considered that since his patient had had syphilis, the lesion might be a gummatous lesion. Dufour and Mourrut,[9] in 1929, and Yater,[10] in 1931, concluded that in their cases the lesions were of lymphatic origin. Lauer,[11] in 1925, and Lambert,[12] in 1940, clearly stated the probable congenital nature of these lesions.

This paper is an attempt to clarify the concept of these cysts and to explain the occurrence of these cysts in the locations in which they are found and their relationship to certain of the diverticula of the pericardium. It is not the purpose of this paper to discuss the mechanisms which might account for changes in the mediastinum or pericardium in association with inflammatory or degenerative disease. The reader is referred to the papers of Kienböck and Weiss,[13] Cushing,[14] and Reitan[15] for extensive collective reviews of mediastinal abnormalities.

To accomplish our purpose we reviewed the cases of cysts of the mediastinum encountered at the Mayo Clinic from June, 1941, to December, 1947, inclusive, and also cysts of the mediastinum and diverticula of pericardium which were reported in the literature.

In order to limit our study to congenital lesions in both series we excluded cases in which any significant pulmonary or cardiovascular disease had been reported in the case record or protocols.

The cases accepted are grouped in Table I in accordance with the type of lesion, the site and type of attachment rather than chronologically, in order to indicate the etiologic mechanism which will be suggested. In the interest of

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TABLE I. PERICARDIAL LESIONS

LESION	AUTHORS	CASES	TOTAL CASES
Diverticulum of pericardium with wide base	Schirmer[24]	1	3
	Lauer[11]	1	
	Bristowe[25]	1	
Diverticulum of pericardium with narrow base	Peacock[26]	1	5
	Coën[5]	1	
	Neprjachin[27]	1	
	Grabowski[8]	1	
	Mazer[20]	1	
Cysts with pedicle to pericardium	Atayas-Maraty[7]	1	7
	Corsini[28]	1	
	Eliaschewitsch[29]	1	
	Bradford, Mahon, and Grow[23] (Cases 5, 7, and 8)	3	
	Pickhardt[1]	1	
Cysts of the cardiophrenic angle	Yater[10]	1	17
	Cabot Case 23492[30]	1	
	Lambert (Berry and Butler)[12]	2	
	Bradford, Mahon, and Grow[23] (Cases 6, 10, 11, and 12)	4	
	Leahy and Culver[31]	1	
	Authors' cases	8	
Cysts located higher in mediastinum with no recorded attachment at cardiophrenic angle	Dufour and Mourrut[9]	1	5
	Authors' cases	4	
Total			37

brevity, the 25 cases from the literature are merely listed as details may be found in the references quoted. The 12 new cases from the clinic are reported briefly.

REPORT OF CASES

CASE 1.—A white man, 64 years old, was first seen at the clinic June 25, 1941. Chief complaint was sacral backache. Routine roentgenograms of the thorax revealed an irregularly rounded mass in the right cardiophrenic angle, which appeared to be distinctly separate from the chest wall and the diaphragm (Fig. 1). No pulsation was noticed on roentgenoscopic examination. Exploration for diagnosis of a possible sacral tumor was performed on July 4, 1941, but no tumor cells were found. On July 17, 1941, another exploratory operation was performed for a possible omental subcostosternal hernia. The diaphragm was normal, but a tumor was felt in the region of the pericardium. On Aug. 27, 1941, the mediastinum was explored and a large cystic tumor was found in the right cardiophrenic angle in the anterior mediastinum. It was adherent to the right mediastinal pleura at the cardiophrenic angle. The cyst was filled with clear fluid. Vessels were ligated in the anterior mediastinum and on the pericardium. The postoperative course was uncomplicated.

Pathologic examination revealed a thin-walled cyst, measuring 9 by 6.5 by 6.5 cm. The walls were composed of fibrous connective tissue lined by flat epithelium.

CASE 2.—A white woman, 61 years old, who was first seen at the clinic Dec. 4, 1942, gave as the chief complaint a tumor in the chest of three and one-half years' duration accompanied by exertional dyspnea and substernal pain on exertion. Roentgenographic examination of the thorax revealed an irregularly rounded mass, completely separated from the diaphragm in the right cardiophrenic angle anteriorly with its broad base to the mediastinum and the

anterior chest wall. There was no pulsation. At operation on Feb. 10, 1943, a large cystic tumor filled with fluid was found beneath the anterior mediastinal pleura attached to the upper one-third of the pericardium and extending anteriorly in front of the arch of the aorta and slightly into the left side of the thoracic cavity. The postoperative course was uneventful.

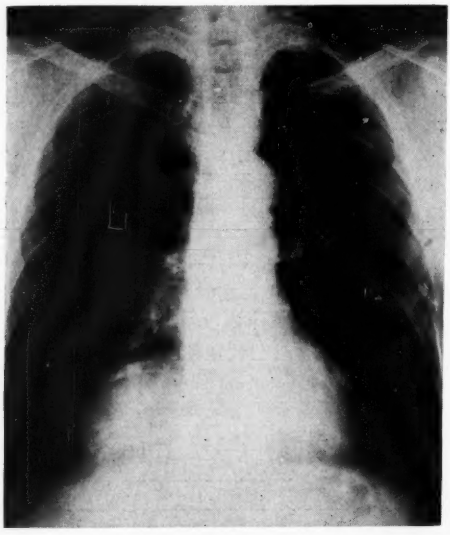

Fig. 1 (Case 1).—Cyst in right cardiophrenic angle.

Fig. 2. (Case 3).—Wall of cyst (hematoxylin and eosin, ×145).

Pathologic examination revealed a cyst approximately 10 cm. in diameter with a thin wall lined by a layer of cells similar to the endothelium of the capillaries in the sections.

CASE 3.—A white man, 29 years old, was first seen at the clinic March 3, 1943. Chief complaint was of a tumor in the chest which had been discovered in a routine roentgenogram while he was applying for a commission in the army. There were no symptoms. Roentgenographic examination revealed a round mass in the right cardiophrenic angle anteriorly. The

mass was separated from the anterior chest wall and the diaphragm. On March 13, 1943, at exploratory operation a cystic tumor was removed from the anterior cardiophrenic angle. The postoperative course was uneventful.

Pathologic examination revealed a simple cyst, measuring 11 by 7.8 by 5.5 cm. The walls were fibrous connective tissue lined by a single layer of very flat cells (Fig. 2). The resemblance to the endothelium of the capillaries is striking.

CASE 4.—The patient who was first seen at the clinic April 15, 1943, gave as the chief complaint a probable thymic tumor, diagnosed in the course of examination for commission in the army. There were no subjective complaints. Roentgenographic examination of the chest revealed a mass in the left upper part of the anterior mediastinum which appeared entirely consistent with a thymoma. The tumor pulsated on roentgenoscopic examination but it could not be determined whether the pulsation was transmitted or not. At operation May 8, 1943, a cystic tumor was found in the anterior mediastinum, a little above the pericardium and extending down over it. The tumor was moderately attached to the extreme upper margin of the pericardium. The deep attachment extended beneath the arch of the aorta.

Pathologic examination revealed a cystic tumor of the mediastinum 11 cm. in diameter, containing clear fluid. The cyst was lined by flattened cells, probably endothelium.

CASE 5.—A white man, 37 years old, who was first seen at the clinic Oct. 6, 1943, had been refused enlistment in the navy because of an "irregularity in the lung." Since that time he had noticed slight dyspnea on exertion. Roentgenographic examination of the thorax at the clinic revealed a rounded shadow at the right cardiophrenic angle anteriorly, not definitely separated from the diaphragm and the chest wall. This was followed for a period of time and did not grow. At operation on May 8, 1944, a thin-walled cystic tumor was enucleated without difficulty from the anterior mediastinum.

Pathologic examination revealed a simple smooth-walled cyst, 11.5 by 9 by 3.5 cm. filled with clear fluid. The cyst was lined with a single layer of flat cells with a remarkable resemblance to the endothelium of the small vessels in the wall of the cyst.

CASE 6.—A white man, 35 years old, was first seen at the clinic Aug. 17, 1944, with the complaints of fluttering of the heart of fifteen years' duration and of pressure on the heart after breakfast. There was no history of exertional dyspnea. He was considered to have paroxysmal tachycardia. Roentgenographic examination of the thorax revealed a rounded shadow anteriorly at the right cardiophrenic angle. There was a slight appearance of separation from the anterior chest wall and the diaphragm. At operation Sept. 28, 1944, a cystic tumor was found at the anterior portion of the right cardiophrenic angle which mesaured 10 by 8 cm. The tumor was removed without difficulty. On pathologic examination the cyst was filled with clear fluid and lined with a single layer of flattened cells. These resembled those of the endothelium of the vessels in the cyst wall.

CASE 7.—A white woman, 55 years old, was first seen at the clinic Aug. 17, 1945. Chief complaints were tachycardia, precordial pressure, and a mass in the mediastinum. For the mass which was discovered two months previously she had received six roentgen treatments without alteration in the size. The pulse rate was 104 beats per minute, blood pressure was 153 mm. of mercury systolic and 100 diastolic. Roentgenographic examination of the thorax revealed a round mass to the left side in the anterior mediastinum at the level of the hilus (Fig. 3). On Aug. 22, 1945, a large cystic tumor attached to the left side of the pericardium and to the superior pericardium and extending into the anterior and superior mediastinum to the left of the superior vena cava to the level of the arch of the aorta was removed. The cyst originated from the pericardium anteriorly.

Pathologic examination revealed a simple thin-walled cyst 6.5 by 6 by 5 cm. The cyst was lined by a single layer of very flattened cells.

CASE 8.—A white man, 30 years old, was first seen at the clinic on Dec. 27, 1945. Chief complaint was a "spot on the lung" which had been discovered on a routine survey for tuberculosis in July, 1945. In November, 1945, the mass seemed to be larger when he con-

sulted a physician in his home locality and he was referred to the clinic for further investigation. Roentgenographic examination of the thorax revealed a rounded mass in the right upper part of the anterior mediastinum, slightly above the level of the aortic arch (Fig. 4). At operation, Jan. 3, 1946, a simple cystic tumor was found in the anterior mediastinum and removed. It bulged into the right side of the thorax anteriorly and superiorly and lay anterior to the superior vena cava, to which it was adherent.

Pathologic examination revealed a simple cyst, lined by a single layer of very flattened cells, resembling endothelium.

CASE 9.—A woman, 56 years old, was first seen at the clinic June 18, 1946, because of "tightening of the chest." Roentgenographic examination revealed a rounded mass at the cardiophrenic angle anteriorly, not definitely separated from the anterior wall of the chest and the diaphragm. At exploratory operation July 25, 1946, a cystic tumor, attached to the pericardium and the pleura, was found at the right cardiophrenic angle and removed.

Fig. 3.

Fig. 4.

Fig. 3 (Case 7).—Cyst in left part of anterior mediastinum.
Fig. 4 (Case 8).—Cyst in right side of the anterior mediastinum.

Pathologic examination revealed a simple cyst, measuring 8 by 5 by 5 cm. and containing 115 c.c. of straw-colored fluid. The cyst was lined by a single layer of cells, resembling endothelium.

CASE 10.—A white man, 36 years old, was first seen at the clinic Jan. 20, 1947. Chief complaint was a dull pain in the right side of the thorax of two and one-half years' duration. Bronchoscopy revealed no intrabronchial tumor. Cytologic study of the sputum revealed no malignant cells. Roentgenographic examination of the thorax revealed a well-circumscribed mass located anteriorly in the right base just above the diaphragm. At exploratory operation March 15, 1947, a cystic tumor was removed from the anterior inferior portion of the thorax (Fig. 5). It was slightly adherent to the diaphragm and to the anterior portion of the pericardium.

CASE 11.—A white woman, 59 years old, was first seen at the clinic Aug. 11, 1947. Chief complaint was a chest tumor which had been discovered during a county tuberculosis survey. There were no significant symptoms. Roentgen examination of the thorax revealed a large tumor of the anterior mediastinum extending into the left pulmonary field. The tumor which was fairly well circumscribed pulsated and moved with respiration. On August 18, a cystic tumor, containing clear fluid, was removed. It extended from the apex of the thoracic cavity on the left to the level of the fourth rib anteriorly, where it was adherent to the pericardium.

Pathologic examination revealed a cystic tumor, filled with clear fluid, which measured 9 by 7 by 5.6 cm. and weighed 209 grams. The cyst was lined with a single layer of flattened cells.

Fig. 5 (Case 10).—Cyst removed.

CASE 12.—A white man, 49 years old, was seen for the first time at the clinic Oct. 17, 1947. Chief complaint was of a chest tumor that had been found on a routine chest survey. He had had dyspnea on exertion for five years. Roentgenologic examination of the thorax revealed a mass in the right cardiophrenic angle. The thorax was explored Oct. 29, 1947, and a pearshaped cyst was found in the anterior mediastinum. The base was attached to the pericardium and the point was at the cardiophrenic angle anteriorly. The cyst was removed without difficulty.

Pathologic examination revealed a cyst, 7 by 5.5 by 4 cm., filled with clear fluid. The cyst was lined by a single layer of flattened cells. Chemical analysis of the fluid from the cyst showed: 50 mg. of sugar, 710 mg. of chlorides, and 0.3 Gm. of protein per 100 c.c.

DEVELOPMENT OF THE PERICARDIUM

The formation of the body cavities from the mesenchyme will be considered generally before certain aspects of the development of the pericardium. The celom arises from splitting of the lateral mesoderm on each side of the body into splanchnic and somatic layers. When the body of the embryo is folded off from the extra-embryonic membranes, the extra-embryonic and intra-embryonic portions of the celom are separated from each other. It is the intra-embryonic portion of the primitive celom which gives rise to the body cavities.

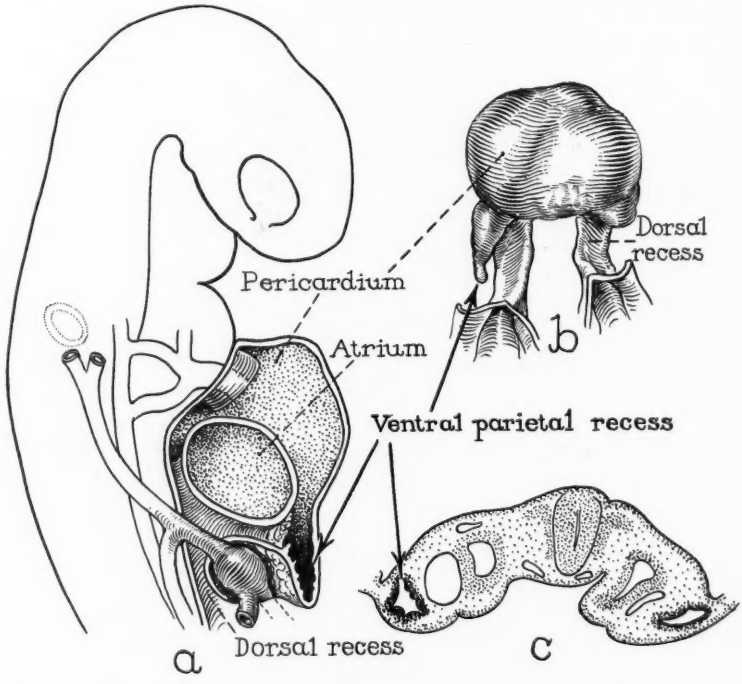

Fig. 6.—*a*, Parasagittal section of a rabbit embryo 9 days old modified from His article. The ventral parietal recess pockets into the septum transversum are illustrated. *b*, (After Davis). The ventral surface of a cast of the pericardial celom of a twenty-somite human embryo illustrating the diverticulum-like appearance of the ventral parietal recesses. *c*, (After Elliott). Transverse section of a ten-somite rabbit embryo, giving another representation of the spatial relationships of the ventral parietal recess.

The pericardial celom is the most precocious of the body cavities. It forms as a horseshoe-shaped cavity about the head of the embryo as a result of the coalescence of the mesenchymal spaces in the celomic cavities on each side of the embryo. This mechanism has had attention brought to it by Lambert.[12] The first step in the division of the body cavities comes with the coalescence of the septum transversum between the limbs of the omphalomesenteric veins from each side. The anlage of the liver forms on the caudal side of this mass, the caudal wall of the pericardium on the cephalic side.

In his original description of the formation of the pericardium and other body cavities, Wilhelm His,[16] in 1881, distinguished two pairs of recesses in the pericardial celom, which he called "the dorsal and the ventral parietal recesses of the pericardial celom." The dorsal parietal recesses are generally known as the "pleuroperitoneal canals" and their role in the formation of the pleural cavities is well understood. The ventral parietal recesses have remained obscure, probably because no significance has ever been attached to them and because they are not well defined in all embryos. However, their presence was shown in the rabbit by Elliott,[17] in 1931, and in the human embryo by Mall,[18] in 1910, and by Davis[19] in 1923. Davis stated, "Besides the pleuroperitoneal openings, the septum transversum possesses a pair of ventral recesses, described by Strahl and Carius and shown by Mall in the human embryo 21 mm. in length." Elliott[17] stated, "With the formation of the septum transversum, the pericardial cavity communicates caudally with the pleuroperitoneal portion of the celom by two constricted canals, the iter venosus of Lockwood or the pleuroperitoneal recesses. The pericardial cavity ends caudally in four of these recesses, the two dorsal and the two ventral pleuroperitoneal recesses—the ventral recesses end blindly at the septum transversum and only the dorsal recesses continue into the pleuroperitoneal coelom." Figure 6 *a*, *b*, and *c* should assist in the development of a spatial concept of the ventral parietal recesses.

RELATION OF THE VENTRAL PARIETAL RECESS TO DIVERTICULA OF THE PERICARDIUM AND TO CELOMIC CYSTS OF THE MEDIASTINUM

We were impressed by the number of cysts which were located at the cardiophrenic angle or were connected to it by a pedicle and were struck by the similarity of the structure of the mesothelial-lined cysts of the mediastinum to that of diverticula of the pericardium in cases in which there was no significant pulmonary or cardiovascular disease. The case of Mazer,[20] in which the lesion was thought even at exploration to be a cyst until it was demonstrated that fluid could be expressed between it and the pericardium suggested strongly that these lesions were related. Since the lesion in so many of the reported cases had a definite relationship to the pericardium at the cardiophrenic angle, it seemed possible that some mechanism other than that proposed by Lambert might be found to account for these lesions.

The discovery that a diverticulum-like structure occurred during development of the pericardium at the site where so many of these lesions were found led to speculation as to their possible relationship. With this in mind, Table II was constructed to show the several possible states in which a ventral parietal recess might be expected to persist and pairing these states with the several states of reported pericardial-celomic cysts and diverticula of the pericardium: The conclusion is difficult to escape that the relationship of the various cysts and diverticula of the pericardium to the several states of persistence of the ventral parietal recess is more than fortuitous. It seems reasonable to conclude that persistence of the ventral parietal recess may be considered as a mechanism which could account for the formation of pericardial-celomic cysts and certain diverticula of the pericardium.

TABLE II. LESIONS WHICH MAY RESULT WHEN VENTRAL PARIETAL RECESS PERSISTS

EMBRYONIC CONDITION	LESION RESULTANT
The ventral parietal recess persists Intact	Diverticulum of pericardium with wide base
Proximal portion is constricted	Diverticulum of pericardium with narrow base
Proximal portion is completely constricted	Cysts with pedicle which extends to pericardium
Is completely pinched off	Cysts in the cardiophrenic angle
Is completely pinched off and left cephalad as the septum transversum moves caudally	Mesothelial-lined cysts found higher in the mediastinum than the cardiophrenic angle

This concept is not completely at variance with the "pulsion diverticulum" theory of Rokitansky.[2] It differs in that it requires the persistence of a definite embryonic structure rather than the pinching off of a hypothetical hernia through a hypothetical weak spot in the pericardium. It has the advantages of not requiring the postulation of a change in the hydrodynamics of the heart and pericardium.

The several other possibilities of cyst formation in the development of the pericardium and pleura may be ignored because the relationship of these lesions to the development of the pericardium, as pointed out by Lambert,[12] is so definite.

PATHOLOGIC ANATOMY

Celomic cysts of the mediastinum are cysts which are composed of fibrous connective tissue, lined by a single layer of flat cells similar to serosal and endothelial cells and which contain clear yellow fluid.

These cysts are found in the anterior mediastinum, usually at one of the cardiophrenic angles. Of the 29 cysts studied (literature and our own) 17 were at the cardiophrenic angles and 7 were connected to the pericardium by pedicles from the cardiophrenic angle. Five cysts were either in the anterior mediastinum at the level higher than the cardiophrenic angles or arose in the anterior mediastinum and extended into the superior mediastinum. Of the 26 cysts for which this information is available, 17 were found on the right side and 9 were found on the left.

The content of these cysts has been described as resembling "spring water" from its translucency and clarity. The contents of several of the cysts in our series were analyzed chemically. The content of protein varied from 0.1 to 0.3 Gm. per 100 c.c., of chlorides from 693 to 710 mg. per 100 c.c., and of fats from 0 to 10 mg. per 100 c.c. The findings of low proteins, high chlorides, low sugar, and low content to absence of fat are characteristics of transudates generally, rather than of exudates or of lymph, according to the criteria of Cantarow and Trumper.[21]

None of these tumors has been found to be malignant.

CLINICAL FEATURES

The salient point in all of the histories of the surgical cases reviewed is that the lesions have been removed at exploration for a circumscribed intrathoracic

lesion. A striking feature of the clinical histories is that in 15 of the 23 cases for which the information is available, the patient had no complaint other than the discovery of a tumor during routine roentgenologic examination of the thorax. Six of the patients complained of epigastric or precordial pain and 2 complained of tachycardia. It is apparent that no symptom complex can be ascribed to the presence of these tumors.

In no case was the lesion suspected as the result of general physical examination.

Roentgenographic Aspects.—In 15 of the 25 cases in which information on the roentgenographic aspects was available the diagnosis of a mediastinal lesion was made as a result of routine roentgenologic examination of the thorax.

Of the lesions for which reports of the roentgenologic examination were available, 18 were on the right side and 7 were on the left. Of the lesions on the right side, 14 (78 per cent) were situated in the region of the cardiophrenic angle and of the lesions on the left side, 3 (42 per cent) were at the cardiophrenic angle. In 17 cases (68 per cent) of the 25 the lesions were located at the cardiophrenic angles.

Lesions in the cardiophrenic angles presented a fairly characteristic appearance. They were well demarcated, rounded or elliptical in form, and homogeneous in density. The lesions followed no rule in separation from the anterior chest wall or from the diaphragm.

Differential Diagnosis.—In no instance has a definite diagnosis of pericardial-celomic cyst or diverticulum of pericardium been made before operation. The reader is referred to the classifications of Heuer and Andrus[22] and of Bradford, Mahon, and Grow[23] for comprehensive review of lesions to be considered in the differential diagnosis of lesions of the mediastinum.

In 2 of the cases in this series, the possibility of a diaphragmatic hernia of the foramen Morgagni type was considered. Inasmuch as the lesions are at the same site, and may have a similar cause, confusion seems inevitable.

Diagnosis and Treatment.—The exact diagnosis of pericardial-celomic cyst or pericardial diverticulum has been made at thoracotomy in the recent cases and at post-mortem examination in the earlier cases. No operative deaths have been reported, and there is no published record of significant postoperative morbidity.

SUMMARY

A collective review of the literature was made for cases of cysts of the mediastinum, filled with a clear fluid and lined by mesothelium and of diverticula of the pericardium in persons who did not have any associated systemic disease which could reasonably have been supposed to have caused these abnormalities. Twelve new cases of pericardial-celomic cysts found in the files of the Mayo Clinic were reported.

The development of the pericardial celom has been reviewed and emphasis placed on the role that persistence of the ventral parietal recess of the pericardial celom may play in the development of these cysts and diverticula.

It has been pointed out that diverticula of the pericardium and celomic cysts of the mediastinum may represent stages in the same developmental process and that they may be considered in this light rather than as separate clinical and pathologic entities.

It is suggested that the exact diagnosis of these cysts and diverticula will continue to be made at surgical exploration since there are no definite diagnostic criteria.

REFERENCES

1. Pickhardt, O. C.: Pleuro-diaphragmatic Cyst, Ann. Surg. **99**: 814-816, 1934.
2. Rokitansky, K.: Quoted by Reitan.[15]
3. Cruveilhier, J.: Quoted by Reitan.[15]
4. Hird: Hernia of the Heart, Lancet **2**: 611, 1848.
5. Coën, E.: Quoted by Reitan.[15]
6. Rohn, A.: Quoted by Kienböck and Weiss.[13]
7. Atayas-Maraty: Quoted by Reitan.[15]
8. Grabowski, Witold: Zur Kasuistik der Perikarddivertikel, Zentralbl. f. allg. Path. u. path. Anat. **37**: 388-391, 1926.
9. Dufour, Henri, and Mourrut: Kyste de la partie supèrieure du pèricarde chez une femme de quatre-vingt-six ans, Bull. et mém. Soc. méd. d. hôp. de Paris **2**: 1482, 1929.
10. Yater, W. M.: Cyst of the Pericardium, Am. Heart J. **6**: 710-712, 1931.
11. Lauer, Woldemar: Zur Kasuistik der angeborenen Perikard-Divertikel, Zentralbl. f. allg. Path. u. path. Anat. **36**: 353-354, 1925.
12. Lambert, A. V. S.: Etiology of Thin-walled Thoracic Cysts, J. THORACIC SURG. **10**: 1-7, 1940.
13. Kienböck, Robert, and Weiss, Konrad: Ueber der entzündliche Pericarddivertikel, Fortschr. a. d. Geb. d. Röntgenstrahlen. **40**: 389-418, 1929.
14. Cushing, E. H.: Diverticulum of the Pericardium, Arch. Int. Med. **59**: 56-64, 1937.
15. Reitan, Häkon: Beitrag zur Röntgendiagnose der Perikarddivertikel und der abgesackten Perikardsexudat, Fortschr. a. d. Geb. d. Röntgenstrahlen. **58**: 195-213, 1938.
16. His, Wilhelm: Mittheilungen zur Embryologie der Säugethiere und des Menschen, Arch. f. Anat., Leipz., Anat. Abteilung., pp. 303-329, 1881.
17. Elliott, Rush: A Contribution to the Development of the Pericardium, Am. J. Anat. **48**: 355-390, 1931.
18. Mall, F. P.: Coelom and Diaphragm. In Keibel, Franz, and Mall, F. P.: Manual of Human Embryology, Vol. 1, Chap. 13, Philadelphia, 1910, J. B. Lippincott Company, pp. 523-548.
19. Davis, C. L.: Description of a Human Embryo Having Twenty Paired Somites (No. 72), Contrib. Embryol. **15-16**: 3-51, 1923.
20. Mazer, M. L.: True Pericardial Diverticulum, Report of a Case With Safe Operative Removal, Am. J. Roentgenol. **55**: 27-29, 1946.
21. Cantarow, Abraham, and Trumper, Max: Clinical Biochemistry, ed. 3, Philadelphia, 1945, W. B. Saunders Company, pp. 258-264.
22. Heuer, G. J., and Andrus, W. DeW.: The Surgery of Mediastinal Tumors, Am. J. Surg. **50**: 146-224, 1940.
23. Bradford, M. L., Mahon, H. W., and Grow, J. B.: Mediastinal Cysts and Tumors, Surg., Gynec. & Obst. **85**: 467-491, 1947.
24. Schirmer, Oskar: Ueber Pericard-Divertikel, Zentralbl. f. allg. Path. u. path. Anat. **34**: 61-64, 1923.
25. Bristowe, J. S.: 3. Warty Growth Upon the Vocal Cords, Tr. Path. Soc. London **19**: 42-43, 1868.
26. Peacock, T. B.: Quoted by Cushing.[14]
27. Neprjachin, G. G.: Zur Frage über das perikardiale Divertikel, Zentralbl. f. allg. Path. u. path. Anat. **39**: 548-551, 1927.
28. Corsini, C.: Quoted by Cushing.[14]
29. Eliaschewitsch, P. A.: Ein Fall von Perikardcysts, Virchows Arch. f. path. Anat. **270**: 868-872, 1929.
30. Cabot Case 23492. Case Records of the Massachusetts General Hospital: New England J. Med. **217**: 958-959, 1937.
31. Leahy, L. J., and Culver, G. J.: Pericardial Coelomic Cyst, J. THORACIC SURG. **16**: 695-700, 1947.